VOLUME 42 NUMBER 5

ARCHIVES OF

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NOVEMBER 1949

SPECIAL NUMBER DEDICATED TO DR. ARNOLD KNAPP

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago.
Under the Act of Congress of March 3, 1879

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THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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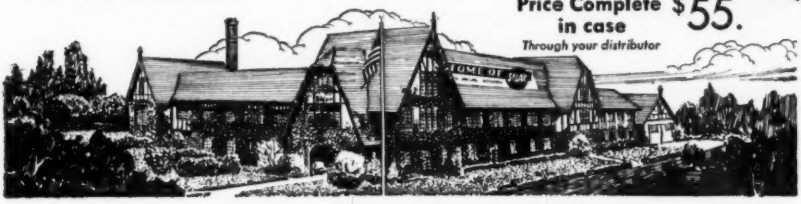

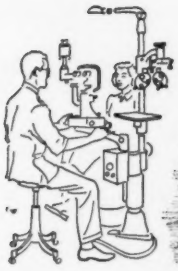

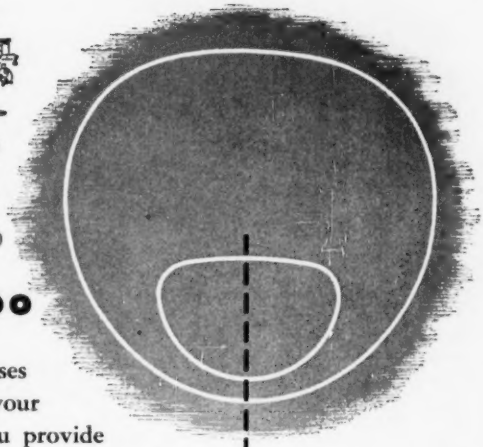

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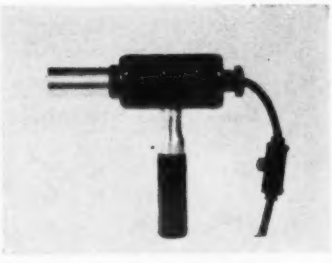

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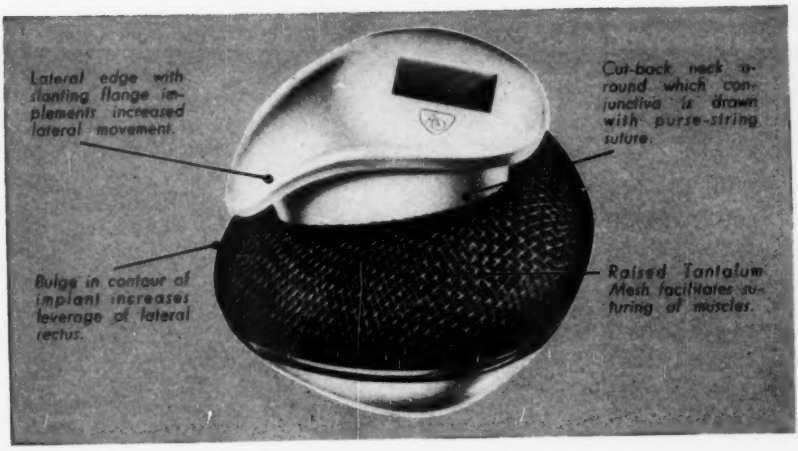
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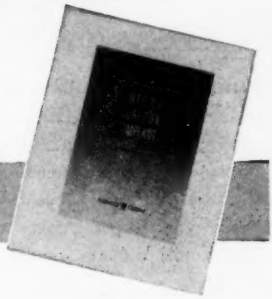

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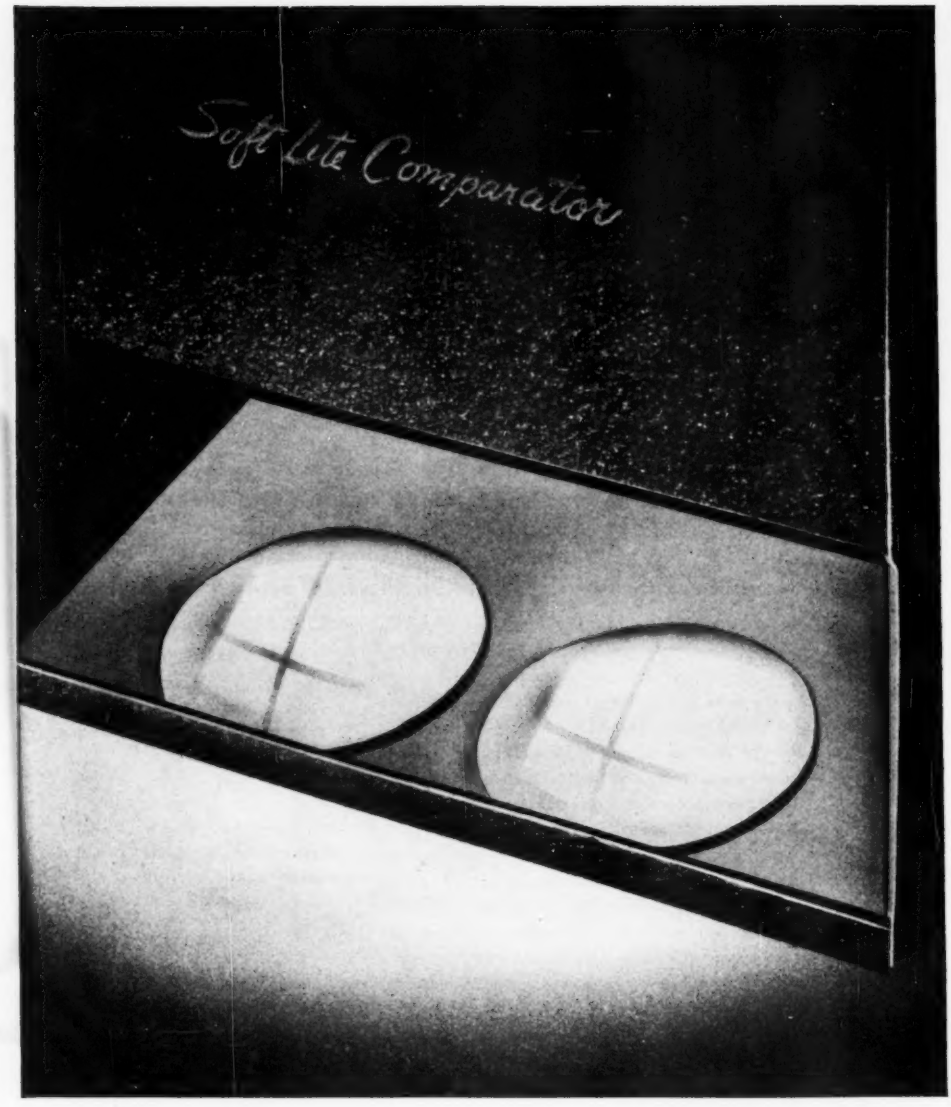

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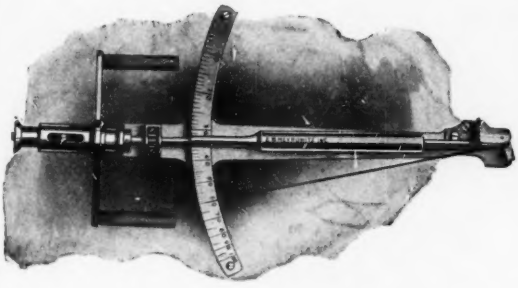

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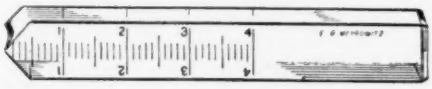

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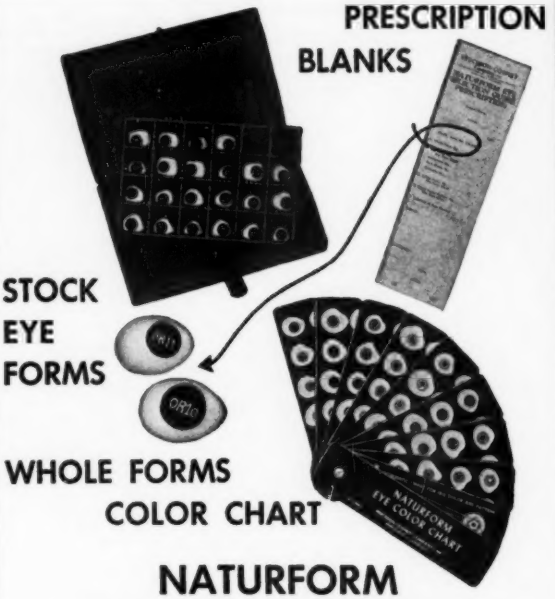

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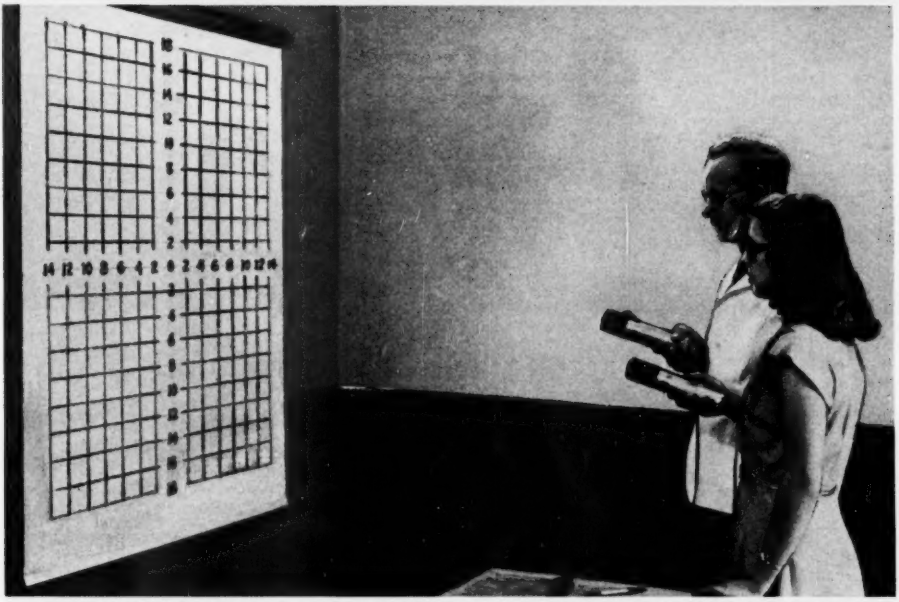

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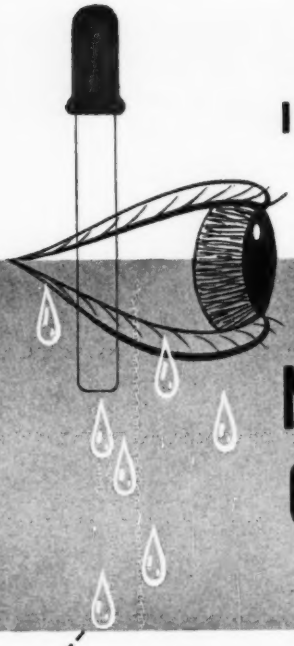

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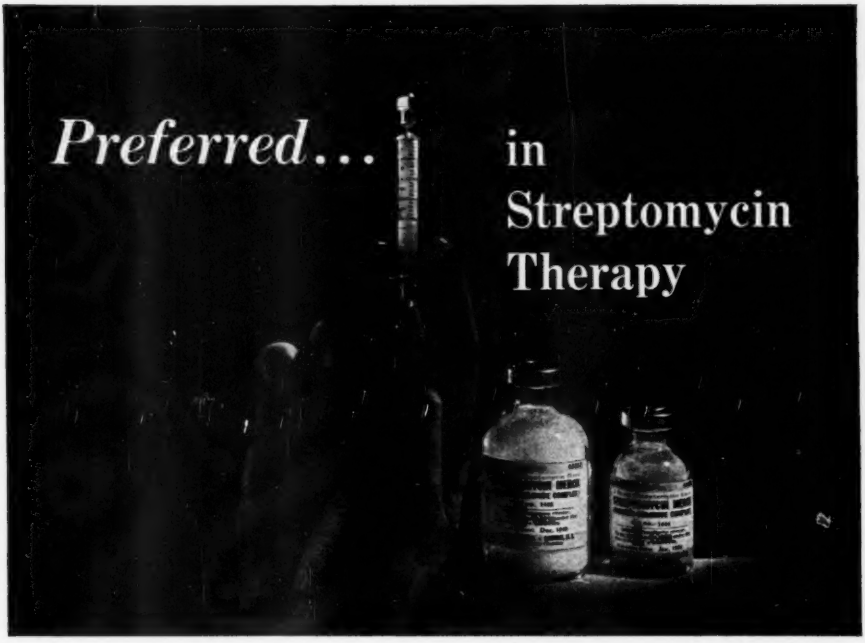

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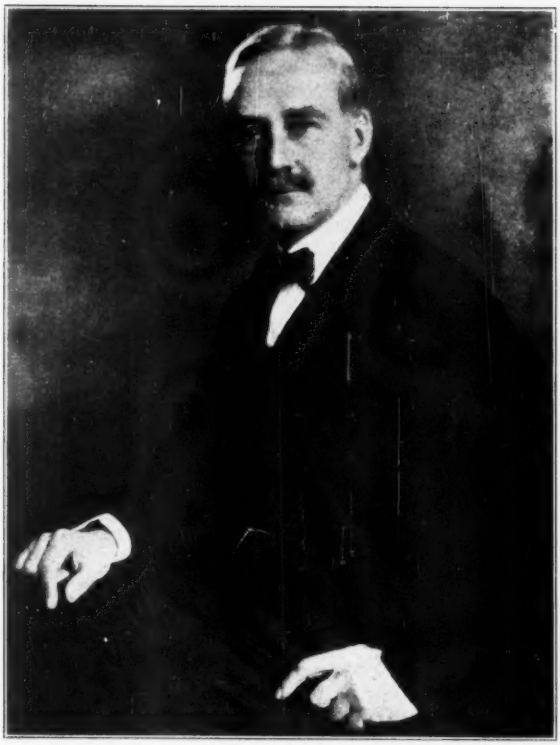

ARNOLD KNAPP, M.D.

FOREWORD

By dedicating this volume to Dr. Arnold Knapp on his eightieth birthday, his colleagues wish to express their esteem and affection for this distinguished ophthalmologist. Born into our specialty, the son of Dr. Herman Knapp, he not only has fostered the sound teachings of his illustrious father, but has greatly enriched ophthalmology by his own efforts. Having been reared in this scientific atmosphere, it is no wonder that he with his inquisitive mind soon became all-absorbed in its search for knowledge—a search that still goes on. Not contented with theories and speculation, he has always devoted his efforts to learning the truth and to stating it in clear words. The ability to winnow the chaff from the grain is an outstanding characteristic of this man. Soundness of judgment, clarity of expression and thorough knowledge of the subject are evidenced in all his writings. To acquire these traits has meant a life devoted unstintingly to study. Ophthalmology is his love, and he has nurtured her well.

After receiving his Bachelor of Arts degree from Harvard in 1889, he entered the Columbia University College of Physicians and Surgeons. Three years later this medical tyro started a surgical internship at Roosevelt Hospital, New York city, with the avowed purpose of becoming a general surgeon. To the loss of surgery and to our great gain, his interest shifted to ophthalmology. After a period of training in European clinics he became associated with his father in the practice of ophthalmology in New York. In these stimulating surroundings he worked assiduously and acquired great clinical experience. At the same time he assessed the pros and cons of his teaching and emerged, not a puppet, but an independent thinker.

The New York Ophthalmic and Aural Institute was the scene of his early activities. This hospital on the lower East Side of New York, which was started by his father in the same year that Arnold was born, was prospering well by the time he began practice. Its staff included Alexander Duane, Ward A. Holden, Charles H. May, H. H. Tyson and John E. Weeks, all distinguished ophthalmologists. Dr. Herman Knapp remained its guiding spirit until 1909, when he was forced to retire on account of ill health. After assuming the position of executive surgeon, Arnold Knapp soon culminated previous plans of his father for expansion of the hospital's facilities by moving into a newly constructed building on Fifty-Seventh Street and Tenth Avenue. With the opening of this institution, on Oct. 1, 1913, its founder was honored by having the name changed to the Herman Knapp Memorial Eye Hospital. In these new surroundings clinical work and postgraduate teaching continued. The scientific atmosphere prevailed, with emphasis on clinical rather than on research activities. After rendering great service to ophthalmology and humanity for over twenty-five years, it merged in 1940 with the Institute of Ophthalmology of the Presbyterian Hospital. With its assets a Knapp Memorial Foundation was created for the advancement of postgraduate study, teaching and research in ophthalmology under the auspices of Columbia University. This fund has supported many of the research activities of

the Institute of Ophthalmology, including the Knapp Research Laboratory, under the direction of Dr. Ludwig von Sallmann, and the Knapp Laboratory of Physiological Optics, with Dr. LeGrand H. Hardy in charge. These two laboratories bespeak the far-reaching interest Dr. Knapp has in scientific ophthalmology.

In 1911 he assumed the editorship of the ARCHIVES OF OPHTHALMOLOGY, which was founded in 1869 by his eminent father. For thirty-eight years he guided its destinies, and for this distinguished service ophthalmology owes him its greatest debt of gratitude. His devotion to its cause did more for the advancement of American ophthalmology than any other one man's efforts. Not only did he critically analyze the contents of each issue but also he added greatly to its prestige by contributing freely articles of his own. His presentations always contain sound clinical observations expressed in clear, concise terms. He not only writes well but edits well. His friendly criticisms of the literary efforts of his colleagues did much to elevate the standard of its articles. The enviable position in ophthalmologic literature held by this periodical is the result of his efforts. For this achievement ophthalmologists the world over salute him.

The arduous duties of this editorship have not deterred Dr. Knapp from assuming other responsibilities. In 1917 he published a volume on "Medical Ophthalmology," a subject which still remains dear to his heart. He has contributed many papers before local and national societies, and his interest continues unabated. His regular attendance at the meetings of the Section of Ophthalmology of the New York Academy of Medicine and the New York Ophthalmological Society is revealing of his love of ophthalmology, as is his frequent presence at the instruction courses given at the meetings of the American Academy of Ophthalmology and Otolaryngology.

For twenty-five years, from 1903 to 1928, he was professor of ophthalmology at Columbia University College of Physicians and Surgeons. On his retirement from active teaching he was appointed professor emeritus. In 1931, in recognition of this long and distinguished service, he was awarded an honorary degree of Doctor of Science by his alma mater. In 1941 the National Society for the Prevention of Blindness awarded him the Leslie Dana Gold Medal. The American Ophthalmological Society honored him with its presidency in 1931; the Section on Ophthalmology of the American Medical Association, with its chairmanship in 1925. In 1946 he delivered the Bowman Lecture before the Ophthalmological Society of the United Kingdom with a most comprehensive and thorough review on "The Present State of the Intracapsular Cataract Extraction." At this time he was elected an honorary member of that distinguished society.

These are but a few of the many honors that have been bestowed on this forthright, clear-thinking, illustrious gentleman, to whom ophthalmology is so much indebted. While we take just pride in his past accomplishments, we rejoice still more in the knowledge that his activities continue. May our debt of gratitude increase for many years to come.

JOHN H. DUNNINGTON, M.D.

ARCHIVES OF OPHTHALMOLOGY

VOLUME 42 NOVEMBER 1949 NUMBER 5

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THERAPEUTIC ACTION OF STREPTOMYCIN AND PROMIZOLE® IN CLINICAL OCULAR TUBERCULOSIS

A Preliminary Report

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THE EXPERIMENTAL background for the use of both streptomycin and promizole® (4,2-diaminophenyl-5′-thiazolsulfone) in treatment of ocular tuberculosis has been presented in previous publications.[1] It was first pointed out [1a] that promizole® had a deterrent action on the course of ocular tuberculosis in the immune-allergic rabbit. This effect became evident after the third week of treatment. There were, however, both clinical and histologic evidences of active disease in the eyes of these treated animals, although much less than in the controls. In the next study,[1b] it was shown that the deterrent action in the normal rabbit, in which there was no immunity and the test therefore was much severer, was much less than in the immune-allergic animal. In the third study,[1c] the therapeutic actions of streptomycin and of the combination of streptomycin and promizole® in the immune-allergic rabbit with ocular tuberculosis were reported. Streptomycin alone had a highly deterrent action on the disease; nevertheless, minimal histologic evidences of active tuberculosis remained in the eyes of the treated animals. The combination of streptomycin and promizole,® however, produced a most dramatic therapeutic result. The eyes of all treated rabbits were free of all clinical evidence of activity after four weeks of treatment, and showed only scarring or the persistence of a few wandering cells on histologic examination. There was only 1 instance of relapse in the animals kept for observation after cessation

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University.

Read at the Fifty-Fourth Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, October, 1949

1. (*a*) Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. The Effect of "Promin" and "Promizole" in Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, Arch. Ophth. **39**:471 (April) 1948; (*b*) XI. Effect of "Promin" and "Promizole" in Experimental Ocular Tuberculosis in the Normal Rabbit, ibid. **40**:1 (July) 1948. (*c*) Woods, A. C., and Wood, R. M.: Studies in Experimental Ocular Tuberculosis: XII. Effect of Streptomycin and "Promizole" in Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, ibid. **40**:413 (Oct.) 1948.

of treatment. For 6 animals culture of the uveal tracts, only 1 showed tubercle bacilli, and on transmission experiments 50 per cent of the uveal tracts of the treated animals were noninfectious, while the uveal tracts of all the untreated controls showed positive cultures and were infectious. It was concluded that the combination of streptomycin and promizole® had a therapeutic action much greater than could be expected from mere summation and that this effect probably was due to a synergistic action—the two agents either attacking separate phases of the metabolism of Mycobacterium tuberculosis or different mutants of the organisms. In the most recent study,[2] it was shown that this combination of streptomycin and promizole® had an equally favorable therapeutic effect in the normal rabbit, indicating that the drugs acted entirely independent of immunity, and quite probably had a direct bactericidal effect on the bacilli.

With the demonstration of the dramatic therapeutic action of these agents in experimental ocular tuberculosis and their relative lack of toxicity in animals, the next step was to apply this form of therapy to ocular tuberculosis in human beings and to evaluate its therapeutic activity.

CHOICE OF PATIENTS

In the application of any form of supposedly specific therapy to ocular tuberculosis, one is always beset with the uncertain nature of the diagnosis. In the absence of tissue for biopsy and material for animal inoculation or from which the bacilli may be isolated, the diagnosis must perforce be presumptive. Therefore, in the evaluation of any new form of therapy, the diagnostic criteria should be unusually rigid.

There were two guiding principles in the choice of patients to be treated. The first principle was that the diagnosis of ocular tuberculosis in any treated patient must be so firm that it would meet the approval of an experienced ophthalmologist. The diagnostic criteria observed were as follows: (*a*) The ocular disease must conform to a pattern commonly regarded as tuberculous, and one in which histologic examination of eyes with similar disease patterns had uniformly demonstrated the probable tuberculous nature of the disease; (*b*) the patient must show elsewhere in the body evidences of a preceding tuberculous infection, a source from which the ocular infection might logically have arisen; (*c*) the cutaneous reactions to tuberculin must be in conformity with those for the patient's age and tuberculous status, and (*d*) the most thorough and exhaustive medical survey possible should reveal no

2. Woods A. C., and Wood, R. M.: Studies in Experimental Ocular Tuberculosis: XIII. Effect of Streptomycin and Promizole on Experimental Ocular Tuberculosis in the Normal Rabbit, to be published.

other systemic disease or cause to which the ocular inflammation could logically be attributed. The details of this diagnostic survey have been outlined elsewhere.[3] The second guiding principle in the selection of patients was that the ocular disease either had not yielded to more conventional forms of therapy or did not appear amenable to such therapy and that the condition of the patient was sufficiently desperate to warrant any risk that this treatment might entail.

Thirteen of the 14 patients whose cases are reported here met these criteria. In 1 case (10) the decision to treat the patient was borderline. While the clinical picture was highly suggestive and the diagnostic survey revealed no probable cause other than tuberculosis, the patient's reactions to tuberculin were almost negative and the only evidence of previous systemic infection was a calcified nodule in the lower lung field. This patient was treated only after consultation with the referring physician on the premise that the diagnosis was more than usually presumptive.

The 14 patients treated with streptomycin and promizole® may be grouped as follows: Three had generalized uveitis, 1 with concomitant scleritis; 4 had classic sclerokeratitis, all with anterior scleritis and pronounced corneal involvement; 1 had diffuse scleritis, both anterior and posterior, with proptosis and limitation of movement of the eye; 4 had severe exudative choroiditis, all with some involvement of the anterior ocular segment with mutton fat keratic deposits and Koeppe nodules, and 2 had hemorrhagic retinitis, or Eales's disease. As already stated, all but 1 of the patients (case 10) appeared to be tuberculous beyond shadow of any reasonable doubt, and there was little probability that any ophthalmologist would have made any other diagnosis in her case.

EVALUATION OF RESULTS

In the evaluation of results, it must be remembered that each observation of a therapeutic response is entirely uncontrolled. In the experimental disease, each treated rabbit is controlled by a rabbit of similar breed, inoculated in a precisely similar manner and maintained under identical conditions. In such controls the course of the untreated disease can be carefully followed, evaluated and compared with the course of the disease in the treated animal. At the end of treatment, tissue is available for histologic examination, culture and transmission experiments. In the human subject no such controls are possible. The judgment of the observing physician that the individual patient under treatment did better than would have been expected in the natural course of events and the summation of such judgments for a number

3. Woods, A. C.: The Etiological Diagnosis of Uveitis, Monograph of the American Academy of Ophthalmology and Otolaryngology, to be published.

of patients is the only method of assaying the value of the therapeutic agents. Thus, the value of any observation is directly proportional to the individual ophthalmologist's knowledge of, and experience with, ocular tuberculosis. This, of course, introduces the human equation.

A second difficulty in evaluating a therapeutic response is the known tendency of ocular tuberculosis to undergo exacerbations and remissions and the resulting difficulty of attributing an improvement to the action of the therapeutic agent. Here, again, it is largely a matter of study and opinion, although the time relation of clinical improvement to the administration of the therapeutic agents may clearly indicate a cause and effect relationship. In the cases here reported the time of the onset of any improvement in relation to the beginning of therapy and the continuity of improvement was carefully considered.

A third difficulty is that a careful distinction must be made between reversible and irreversible changes in the eye. All any therapeutic agent can do is to destroy or immobilize the causative organism of the disease. If the disease is still in the infiltrative stage and tissue destruction or permanent inhibition of nutrition has not occurred, the destruction or fixation of the causative agent will be followed by a return of function. However, if irreversible changes have already taken place, little or no improvement in function can be expected. Among such irreversible changes in the eye would be the presence of corneal scars; the existence of organic adhesions with their destructive sequelae; interference with the nutrition of the lens with resultant incipient cataract, which may reasonably be expected to progress to maturity even though the underlying disease is controlled; the presence of heavy vitreous opacities, which may shrink over a long period but are, nevertheless, more or less permanent, and the actual destruction of the percipient elements of the retina with secondary gliosis. Therefore, at the beginning of therapy such organic changes should be carefully noted and estimated, and their persistence, after termination of therapy and the control of all inflammatory manifestations of the disease, should not be regarded as evidences of the failure of the therapeutic agent.

ADMINISTRATION OF THERAPEUTIC AGENTS

The proper dose and methods of administration of new agents are largely matters of clinical observation. Fortunately, with both streptomycin and promizole® considerable accurate information was already at hand. The report of the Veterans Administration to the Council of Pharmacy and Chemistry of the American Medical Association [4]

4. The Effect of Streptomycin on Tuberculosis in Man, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **135**:634 (Nov. 8) 1947. Dosages of Streptomycin in Tuberculosis, Current Comment, ibid. **133**:842 (Nov. 29) 1947.

showed that in man equally good therapeutic effects with streptomycin were obtained when the antibiotic was given in doses of 0.5 Gm. every twelve hours as when similar doses were given every six hours or oftener. Further, with this dose the toxic effects were considerably less, involvement of the vestibular branch of the eighth nerve occurring in only 17 per cent of persons so treated, whereas it occurred in 96 per cent of patients receiving 2.0 Gm. or more a day. This finding of a similar therapeutic response to smaller doses given at greater intervals is also in conformity with Feldman's experimental results.[5] As concerns promizole,® it had been found that a satisfactory therapeutic response was achieved in experimental animals with blood levels of from 1.5 to 2.0 mg. per hundred cubic centimeters, and this observation had been confirmed in cases of human systemic tuberculosis in which a similar treatment was given. Blood levels of this magnitude are readily obtained in man by the administration of 6 Gm. of promizole® a day in divided doses. In the light of this information, these doses were adopted for the treatment of ocular tuberculosis in the patients here reported, i. e., 0.5 Gm. of streptomycin administered intramuscularly every twelve hours and 6.0 Gm. of promizole® given orally in divided doses. With this dosage, the promizole® level of the plasma varied from 1.2 to 2.5 mg. per hundred cubic centimeters. Since these doses gave a minimum of toxic reactions combined with an eminently satisfactory therapeutic response, they were in general given to all patients, with 2 exceptions (cases 12 and 13). The newer dihydrostreptomycin hydrochloride was used in treatment of the last 7 patients, with an equally favorable therapeutic response. In passing, it may be noted that recent unpublished reports do not indicate a lessened toxicity of this preparation, but, rather, demonstrate a deferred toxic action. It is worthy of note, however, that 1 patient in this series (case 8) who had previously abandoned streptomycin therapy on account of evidences of vestibular irritation was later able to take the dihydro salt without any toxic symptoms.

To the first patient treated, streptomycin was first given alone, and promizole® was added only two weeks before cessation of the streptomycin therapy. This patient was treated before the synergistic action of the two agents had been demonstrated, and therapy was planned with the idea that the promizole® would be continued after a full course of treatment with streptomycin (120 Gm.). To the second patient, promizole® alone was given for a period of seven months, and streptomycin was added only when the patient had an exacerbation.

5. Feldman, W. H.; Hinshaw, C. H., and Karlson, H. G.: Frequency of Administration of Streptomycin: Its Influence in Results of Treatment of Tuberculosis in Guinea Pigs, Am. Rev. Tuberc. **55**:435 (Oct.) 1947.

To all other patients, streptomycin and promizole® were given synchronously, and the combination was continued until what was considered a "full course" had been given or the occurrence of toxic symptoms indicated that one or the other agent should be withdrawn.

The total proper doses of streptomycin and promizole® for ocular tuberculosis are still undetermined both in experimental animals and in man. On the basis of the information gleaned from experimental observations, and the published clinical reports on the amounts of streptomycin used in treatment of systemic human tuberculosis, it was first decided that a "full course" of streptomycin for ocular tuberculosis in man would be equivalent to a dose somewhere between 120 and 200 Gm. Inasmuch as definite clinical improvement was noticed after the administration of much smaller amounts, and one was naturally fearful of vestibular damage with the prolonged use of streptomycin, it was decided to cut the total dose of streptomycin first to 65 Gm. and later to 42 Gm. if these amounts could be taken without toxic symptoms. Certainly, satisfactory immediate clinical results were obtained with as little as 26 Gm. of streptomycin combined with 156 Gm. of promizole,® but whether or not these results will be permanent, or whether the patient will later show recurrences, remains to be seen. For the present, until more information is available, it would appear that when streptomycin is given with promizole® a total dose of 42 Gm. of streptomycin given in doses of 0.5 Gm. twice daily would be sufficient in all but especially severe and resistant cases. As far as promizole® is concerned, the drug is relatively nontoxic in doses of 6 Gm. a day. When toxic symptoms appear, they are quite definite—fever, vertigo, anorexia, malaise, leukopenia and dermatitis—and they disappear immediately on withdrawal of the drug. Therefore if the drug is being well tolerated, and there appears to be any clinical indication for its further use, there is little reason that it should not be continued after the course of streptomycin is completed. However, in the cases here reported, a total of 250 Gm. appeared adequate, although many patients took far greater amounts. It might be noted that a red color of the urine is the rule in promizole®-treated patients and should not be considered a toxic reaction.

RESULTS

The pertinent data on the cases and the therapeutic results are given in the accompanying table. Summaries of the 14 case histories are presented at the end of the paper.

Therapeutic Response.—In all of the 14 cases here reported there was complete resolution of all inflammatory symptoms. In 1 instance (case 12) the patient arbitrarily reduced the dose of streptomycin to

0.5 Gm. once a day, and the condition did not completely clear up with this dose. However, when the dose was increased to 1.0 Gm. a day there was complete clearing in three weeks.

The first evidence of change for the better was observed from nine days to three weeks after the beginning of treatment, and the improve-

Data on Treatment of Patients with Ocular Tuberculosis with Streptomycin and Promizole®

No.	Age, Yr.	Diagnosis	Duration and Amount of Treatment		Toxic Reactions		Results
			Strepto-mycin	"Promizole"	Strepto-mycin	"Promi-zole"	
1	55	Scleritis, uveitis	5 mo. 120 Gm.	3½ mo. 676 Gm.	+	+	Complete subsidence of all inflammation; mature cataract
2	48	Choroiditis	42 days 42 Gm.	17 mo. 2,250 Gm.	+	None	Complete subsidence of choroiditis; vision improved from 20/100 to 20/30+
3	38	Uveitis	34 days 34 Gm.	8 mo.	+	None	Complete subsidence of all inflammation; mature cataract
4	55	Bilateral sclero-keratitis	30 days 39 Gm.	16 days 98 Gm.	None	+	Complete subsidence of inflammation; vision rose from 1/200 to 8/200
5	26	Choroiditis	6 wk. 80 Gm.	6 wk. 300 Gm.	None	None	Complete resolution of choroidal exudate; vision rose from 10/200 to 20/30
6	56	Uveitis	5 mo. 152 Gm.	5 mo. 900 Gm.	None	None	Complete subsidence of all inflammation; mature cataract
7	49	Bilateral sclero-keratitis	26 days 26 Gm.	26 days 156 Gm.	Slight	Slight	Subsidence of inflammation; no change in vision
8	48	Choroiditis	37 days 37 Gm.	60 days 480 Gm.	None	None	Subsidence of inflammatory symptoms; vision rose from 3/200 to 12/200
9	61	Sclerokeratitis	65 days 65 Gm.	31 days 252 Gm.	None	+	Complete subsidence of all inflammation; vision rose from counting fingers to 20/20 —1
10	24	Choroiditis	42 days 42 Gm.	42 days 252 Gm.	None	None	Presumptive diagnosis; arrest of progression and subsidence of inflammatory symptoms; no change in vision
11	24	Scleritis	40 days 40 Gm.	67 days 400 Gm.	None	None	Complete subsidence of all inflammation; vision rose from 20/30 to 20/20
12	24	Sclerokeratitis uveitis	112 days 84 Gm.	91 days 504 Gm.	None	+	Regression of original lesions and improvement of vision from 20/100 to 20/40; one area of scleritis persisted after administration of 63 Gm. but cleared completely after a total dose of 84 Gm.
13	37	Hemorrhagic retinitis	42 days 168 Gm.	42 days 252 Gm.	None	None	Absorption of hemorrhages; vision in right eye rose from 1/200 to 20/100; vision in left eye improved from 20/50 —1 to 20/40
14	31	Tuberculous periphlebitis of retina	42 days 42 Gm.	42 days 252 Gm.	None	None	Absorption of hemorrhages; vision in right eye rose from finger counting to 20/30; vision in left eye declined from 30/50 to finger counting and then improved to 6/200 on discharge

ment steadily continued after cessation of treatment until the eyes showed no evidences of any activity. However, irreversible changes did not disappear; vitreous opacities remained, although vitreous haze cleared and the opacities became more circumscribed (cases 2 and 8). In 3 cases (1, 3 and 6) lenticular opacities already well advanced when treatment was started progressed steadily until the cataracts became mature. In cases 4 and 7, with heavily scarred corneas, there were

no changes in vision, although all evidences of inflammation disappeared. These cases may all be taken as instances of irreversible changes in the eye. In all the remaining cases there was not only complete clearing of all clinical evidences of active inflammation but also a considerable restoration of vision. This varied from a minimum improvement of from 3/200 to 12/200, with irreversible opacities in the vitreous, in case 8, to a maximum impovement of from finger counting at 2 feet (60 cm.) to 20/20 — 1, in case 9. In the latter case the initial visual loss was due to early, unorganized infiltrates in the cornea, a reversible change.

The conspicuous finding in relation to the therapeutic response was the uniform, and apparently complete, control of the clinical evidences of inflammation. In the limited period of observation after cessation of treatment there have been no recurrences. The period of observation, however, has been too short to justify any conclusion on this point. However, the indications, from the evidence at hand, are that these agents have a therapeutic action in human ocular tuberculosis quite comparable to their effect in experimental animals—certainly a bacteriostatic, and probably a bactericidal, effect.

Toxic Reactions.—Streptomycin: All patients given streptomycin were warned of the possibility of vestibular symptoms and were instructed to discontinue use of the drug on the appearance of any vertigo. Patients under immediate control were examined each week by an otolaryngologist for any evidences of vestibular irritation, and patients not under immediate control were instructed to have similar examinations made by their local specialists.

In 4 cases (1, 2, 3 and 7) evidences of vestibular irritation developed with streptomycin therapy. In 1 case symptoms developed with streptomycin, but the patient later took dihydrostreptomycin without reaction. In every case the symptoms disappeared after the drug was withdrawn. There was no instance of any residual damage to the vestibular tract and no persisting aural symptoms. With the precautions of warning the patient, weekly aural examinations and immediate withdrawal of the antibiotic on any evidence of vestibular irritation, there appears to be no significant danger in the use of streptomycin.

Promizole®: In 4 cases (1, 4, 9 and 12) definite toxic reactions to promizole® occurred. In case 1 the patient took 600 Gm. of promizole® without reaction over a three and one-half month period and then exhibited weakness and malaise. The icterus index was found to be 17.2. Promizole® was discontinued, and there was prompt recovery. Two weeks later the patient recommenced use of the drug and then took 76 Gm., without symptoms. She then again complained of weak-

ness and dizziness. The icterus index at this time was 12, and the result of the Hanger flocculation test was positive. Promizole® was then permanently discontinued, with prompt recovery from all toxic symptoms. In case 4 dermatitis developed; this subsided when promizole® was withdrawn and recurred when it was again given. Patient 9 was hospitalized in the Wilmer Institute during treatment. After receiving 140 Gm. of promizole,® she had an unexplained fever and relative leukopenia. Promizole® was stopped, with prompt disappearance of all symptoms. Fever and leukopenia recurred when promizole® was again given, after a week's rest. The drug was then permanently discontinued, with prompt subsidence of the fever and a rise in the white cell count to normal. In case 12 relative anemia and leukopenia developed after administration of 500 Gm., and the drug was permanently discontinued. In another case (7) the patient experienced slight symptoms, consisting of lassitude, headache and anorexia, after taking 156 Gm. of promizole.® Symptoms promptly disappeared after withdrawal of the drug, and promizole® was not again given. The occurrence of toxic reactions to promizole® did not appear to be related to any undue concentration of the drug in the plasma. Similarly, there was no indication of undue retention of the drug, the maximum plasma level obtained being 2.8 mg. per hundred cubic centimeters. In all other cases promizole® was administered without symptoms of any kind, and in 1 case (2) the patient continues to take small daily doses as a precautionary measure and has now received a total of over 2,000 Gm.

Relation of Toxic Symptoms to Total Dose.—Streptomycin: In no case was evidence of vestibular irritation noticed until a minimum total dose of 26 Gm. had been reached. Other total doses for patients showing toxic symptoms were 34, 42 and 120 Gm. In all cases in which reactions occurred, the clinical improvement preceded the occurrence of the toxic symptoms. Thus, in case 7, with the minimum dose of 26 Gm. combined with 156 Gm. of promizole,® an excellent therapeutic response had been obtained before any toxic symptoms appeared.

Promizole®: The patients showing reactions to promizole® received from 98 to 600 Gm. before any toxic symptoms were noted. In each of these patients there had already been a satisfactory response to the treatment, which continued after the drug was withdrawn.

The evidence so far amassed indicates that while toxic reactions occur in a large percentage of patients treated with streptomycin and promizole,® in no instance so far observed have the symptoms been severe or followed by any permanent residua. Moreover, in all instances the toxic symptoms were delayed and did not occur until a satisfactory therapeutic response had been obtained. It would appear therefore that with proper precautions the combined treatment with streptomycin

and promizole® is reasonably safe. Since toxic reactions appear to be delayed, a therapeutic response may be expected before any toxic manifestations occur.

COMMENT

The cases here reported represent my total personal experience with the treatment of clinical ocular tuberculosis with streptomycin and promizole® up to July 27, 1949. The small number of patients treated is explained by the rigidity of the criteria for selection, namely, that the primary diagnosis be almost unquestioned and that the condition be of sufficient seriousness to justify treatment. The number of cases is admittedly too few, and the period of post-treatment observation too short, to permit valid conclusions. This report must therefore be considered a preliminary one. However, the material at hand does indicate a remarkable therapeutic effect for the combination of streptomycin and promizole® in clinical ocular tuberculosis—namely, that toxic reactions are frequent but are comparatively mild, and that there is a reasonable expectancy for a therapeutic response before any toxic reactions become manifest. In short, there appears to be sufficient evidence for a more widespread use of these agents in treatment of tuberculosis of the eye.

A more widespread use must of necessity be followed by some unfavorable reports. There is no evidence whatsoever that these preparations are of the slightest value in any forms of endogenous ocular disease other than those caused by Mycobacterium tuberculosis. The difficulty in establishing a diagnosis of ocular tuberculosis has been mentioned here and explored at length elsewhere. Both the clinical and the experimental forms of ocular tuberculosis mimic the changes produced by other granulomatous diseases—syphilis, brucellosis, sarcoidosis, virus diseases, fungous disease—to an amazing degree. Since it is virtually impossible to establish conclusively the diagnosis of ocular tuberculosis by clinical examination alone, the most thorough and exhaustive medical survey is necessary to confirm the clinical impression. Even with such a complete survey, the final diagnosis is often somewhat uncertain. Therefore, it follows that if these agents obtain any widespread use by ophthalmologists, there is the probability they may be used for the treatment of other than tuberculous ocular disease. If the disease fails to respond to treatment, the failure will probably be attributed to the ineffectiveness of the therapeutic agents, although it may in truth be the result of an incorrect original diagnosis. The meager evidence at hand indicates that the absence of a therapeutic response to these agents in a case of supposed ocular tuberculosis might argue against the tuberculous nature of the disease, just as failure to respond to arsphenamine or penicillin argues against a syphilitic etiology. However, the available

evidence for absolute specificity in ocular tuberculosis is still too slight to warrant such a sweeping assumption. Further, it has been demonstrated that some strains of Myco. tuberculosis are naturally resistant to streptomycin. At present, the wisest course would be to limit the use of these preparations to frank or probable cases of ocular tuberculosis, and not to use them in cases of doubtful etiology. Only by this means can a respectable body of evidence for or against their efficacy be accumulated. All that can be said at this time is that streptomycin and promizole® have a proved and remarkable therapeutic effect in experimental ocular tuberculosis both in the immune-allergic and in the normal animal, and that the meager evidence at hand indicates a no less dramatic effect in ocular tuberculosis in man.

CONCLUSIONS

1. Streptomycin given in doses of 0.5 Gm. twice daily combined with promizole® in the amount of 6 Gm. a day in divided doses had a dramatic effect in controlling the clinical evidence of activity and inflammation in the 14 patients with frank ocular tuberculosis so treated.

2. A therapeutic response was observed after nine to twenty-one days of treatment. The response thereafter was slow but steady.

3. Irreversible changes, such as corneal scarring, cataracts, vitreous opacities and organic tissue damage, were not influenced by such treatment. Reversible changes—corneal infiltrates, nodules in the iris, choroidal exudates and all inflammatory changes—regressed.

4. Toxic symptoms appeared in a large percentage of patients so treated. These symptoms were not serious and, if the drugs were discontinued, promptly disappeared without residua.

5. A therapeutic response was manifest before the appearance of any toxic manifestations.

SUMMARY OF CASES

The protocols of the 12 cases are briefly summarized.

CASE 1 (referred by Dr. Charles Young).—A white woman aged 50 was first seen in May 1945. The family history was noncontributory, and the past history was also unremarkable except for a mastectomy in 1933. On admission she presented generalized granulomatous uveitis and scleritis in the right eye, the left eye being normal. Medical survey at that time was essentially noncontributory except for a pronounced hypersensitivity to tuberculin. She was placed under tuberculin therapy, but it proved almost impossible to desensitize her on account of systemic and focal reactions. The condition of her right eye became steadily worse, and in 1946 the eye was enucleated as blind, painful and phthisical. Histologic examination showed diffuse tuberculous uveitis. Uveitis and scleritis developed in the left eye in 1946. Despite nonspecific treatment and administration of as much tuberculin as could be tolerated, the disease progressed; and in October 1947 there were advanced uveitis and scleritis with lenticular opacities and the

prognosis appeared almost hopeless. Streptomycin was given over a five month period, the total dose being 120 Gm. Its use was discontinued on account of toxic symptoms. Treatment with promizole® was started two weeks before cessation of streptomycin and was continued for three months, the total dose being about 600 Gm. Toxic symptoms then developed, and promizole® was discontinued. However, while the patient was still under treatment with streptomycin the eye began to clear, and improvement thereafter was steady, until in December 1948 there was no trace of inflammation. The lenticular opacities, present when first seen, progressed to a mature cataract, which was successfully removed on July 11, 1949.

Case 2 (referred by Dr. M. E. Randolph).—A white physician aged 45 was first seen in December 1947. The family and past histories were noncontributory. Vision in the right eye had begun to fail two months previously. Examination showed extensive choroiditis in the temporal portion of the fundus with definite evidences of involvement of the anterior uvea. The left eye was normal. The medical survey was entirely noncontributory except for roentgenographic evidence of old extensive pulmonary tuberculosis. There was pronounced hypersensitivity to tuberculin. The condition became progressively worse despite nonspecific protein therapy and local diathermy. Vision was reduced to 20/100. The patient was placed first under treatment with promizole® alone, and the condition slowly improved for seven months, vision rising to 20/30. There was a sharp relapse after seven months' treatment with promizole® alone, and streptomycin was then added, followed by a prompt response after three weeks' treatment. Use of streptomycin was continued for forty-two days and then abandoned on account of vestibular irritation. Promizole® therapy was continued on a reduced dose of 4 Gm. a day. By December 1948 the choroiditis was quiet, and on April 1, 1949 vision was 20/30 + and there were no evidences of any activity. The anterior uvea appeared entirely normal. The patient continues to take promizole® as a precautionary measure. The total dose of streptomycin was 42 Gm. and the total dose of promizole® is now over 2,000 Gm.

Case 3.—A white woman aged 30 was first seen in 1941 with exudative choroiditis of the left eye. Medical survey showed evidence of old pulmonary tuberculosis and violent hypersensitivity to tuberculin; otherwise it was noncontributory. The initial attack of choroiditis quieted under tuberculin therapy, which was discontinued after ten months; but four years later tuberculin was again given over an eight month period for a recurrence in cutaneous sensitivity without ocular recurrence. There was a recurrence of choroiditis in January 1948. Tuberculin therapy was again recommended. The patient apparently received excessive doses, and violent focal reactions ensued. She was seen again in March 1948. At that time there was violent active generalized uveitis of the left eye with reduction of vision to finger counting at 2 feet (60 cm.). The lens was opaque. Streptomycin and promizole® were given. The streptomycin was continued for thirty-four days (34 Gm.) and then discontinued on account of vestibular irritation. Promizole® was continued for eight months, the total dose being 1,410 Gm. There was a steady and complete subsidence of all inflammation. There was no improvement of vision, and on last examination, in April 1949, the eye was white and free of all inflammation, tension was normal and there was a mature cataract. Vision was reduced to light perception and good projection. The right eye remained normal.

Case 4 (referred by Dr. Angus MacLean).—A white woman aged 55 was first seen in May 1948. The family and past medical histories were noncontributory.

The patient gave a history of recurrent bilateral sclerokeratitis since the age of 13 years. She had received tuberculin therapy over a fourteen month period in 1943-1944, with some beneficial results. On examination, the process in the right eye appeared inactive with old corneal scars, and the left eye showed a highly active sclerokeratitis and old scars. Vision was reduced to 1/200. The medical survey was again entirely noncontributory except for pronounced hypersensitivity to tuberculin and roentgenographic evidence of old, inactive pulmonary tuberculosis. Treatment with streptomycin and promizole® was started on June 2, 1948 and was continued for one month, the promizole® being discontinued because of dermatitis, which cleared when promizole® was withdrawn and recurred when it was again given. The total dose of streptomycin was 42 Gm., and the total dose of promizole,® 98 Gm. Subjective improvement was striking from the beginning of treatment; the examining ophthalmologist reported that monthly examinations showed excellent clinical improvement, subsidence of inflammation and clearing of corneal infiltrates. By November the eye was white and the disease inactive. Vision had risen to 8/200. The old corneal scars were unaffected.

Case 5 (referred by Dr. Angus MacLean).—A white man aged 26 was first seen in October 1948. The family and past medical histories were noncontributory. In 1944 both eyes had been the site of repeated attacks of choroiditis, which had spared the macula. He had received tuberculin for three years, from 1945 to 1947, but was able to tolerate only low doses. In April 1948 a small exudative choroidal lesion developed in the left eye just nasal to the macula; this lesion cleared quickly, leaving the eye with 20/15 vision. There was recurrence in the left eye in August, and the eye did not yield to nonspecific protein or tuberculin therapy. When examined in October, the right eye showed scars of old inactive choroiditis and 20/20 vision. The left eye showed atrophic scars from the former attacks and a large active exudative lesion in the macula. Vision was reduced to 10/200, eccentrically. The medical survey was noncontributory except for extreme hypersensitivity to tuberculin and roentgenographic evidences of an inactive pulmonary lesion. Combined treatment with streptomycin and promizole® was started on Oct. 27, 1948 and continued until the patient had received a total of 80 Gm. of streptomycin and 300 Gm. of promizole.® Definite clinical improvement was noted two weeks after onset of treatment. The improvement steadliy continued, and at the end of the seventh week the choroidal infiltrates had subsided. On last examination the eye appeared free of all evidence of active disease, showing only old pigmented scars. Vision had risen to 20/30, from the initial low of 10/200.

Case 6.—A white woman aged 56 was first seen in June 1948. The family and past histories were noncontributory. Visual symptoms first developed in the left eye in November 1947. Examination in June 1948 showed that the right eye was normal throughout and revealed extensive exudative choroiditis in the left eye, with Koeppe nodules, mutton fat keratic deposits and mild evidence of involvement of the anterior uvea. Vision was reduced to perception of hand movements. Opacities were noted in the posterior cortex of the lens. A complete medical survey was noncontributory except for roentgenographic evidences of old pulmonary tuberculosis and a moderate sensitivity to tuberculin (0.1 mg.), compatible with her age. She was placed under treatment with streptomycin and promizole® on Aug. 21, 1948, and this treatment was continued steadily except for a twelve day remission (November 23 to December 5). On December 14, after 102 Gm. of streptomycin and 600 Gm. of promizole® had been given, the inflammatory signs in the anterior uvea had completely disappeared. Treatment was

continued until Feb. 4, 1949, the total dose of streptomycin being 152 Gm. and the total dose of promizole® 900 Gm. In February 1949 the eye was entirely quiet; there was no sign of any inflammatory reaction, but the cataract noted on first examination had slowly matured. Vision was reduced to light perception and good projection.

Case 7.—A white woman aged 49 had been under observation for recurrent bilateral sclerokeratitis since 1931. The family history was noncontributory, and the past history was also without significance except for a pulmonary lesion in girlhood and a history of recurrent bilateral sclerokeratitis since the age of 17. On first examination (1931) vision was 20/50 in the right eye and 20/15 in the left eye. Both eyes showed pronounced peripheral scarring of the cornea, and there was active sclerokeratitis of the right eye. The medical survey was noncontributory except for roentgenographic evidence of inactive old pulmonary tuberculosis and pronounced hypersensitivity to tuberculin. The results of brucella studies were all negative in 1931 but became positive in 1945, when the patient had an unexplained intermittent fever. From 1931 to 1948 there were repeated attacks of sclerokeratitis in both eyes, especially the right. The patient received repeated courses of tuberculin, followed by ocular improvement, but complete desensitization to tuberculin could never be attained. Local diathermy and nonspecific protein therapy had no effect on the ocular inflammation. There was transient improvement under beta irradiation. In October 1947 a severe attack occurred in the right eye, and the condition did not respond to any form of therapy. By August 1948 vision was reduced to light perception and the condition of the eye was so critical that enucleation was considered. Treatment with streptomycin and promizole® was started on Aug. 10, 1948. Within two weeks improvement was noticeable and continued steadily thereafter. All treatment was stopped on Sept. 6, 1948 because of mild vestibular irritation and toxic symptoms. The patient received a total of 26 Gm. of streptomycin and 150 Gm. of promizole.® The improvement continued steadily after cessation of treatment, and by October 1948 the eye was free of any active inflammation. There was no visual improvement because of heavy corneal scarring. There have been no recurrences in a ten month period of post-treatment observation. Degenerative calcareous deposits have occurred in the cornea.

Case 8 (referred by Dr. Arnold Knapp).—A white woman aged 48 was first seen in December 1948. The family history was noncontributory. There was a past history of cervical adenitis as a child and of a circumscribed choroidal lesion in the right eye ten years previously, the latter healing under tuberculin therapy. The present illness began in August 1948; it was characterized by severe recurrence of the choroiditis in the right eye with evidence of involvement of the anterior uveal tract. Penicillin and nonspecific protein therapy were given, without avail. Streptomycin and promizole® therapy had been given in New York over a twenty-three day period, without apparent improvement, and was discontinued on account of toxic symptoms. Examination in December 1948 revealed extensive granulomatous uveitis of the right eye with reduction in vision to 3/200; no fundus details were visible on account of the clouding of the vitreous. The medical survey in New York and Baltimore was noncontributory except for roentgenographic evidences of an old inactive tuberculous lesion in the right outer lung field and pronounced hypersensitivity to tuberculin. Dihydrostreptomycin was now given with promizole,® the combined therapy being started on Feb. 14, 1949 and continued for thirty-seven days, without toxic reaction. Treatment was followed at

this time by clearing of all signs of inflammation of the anterior segment, relative clearing of the vitreous to the point where the fundus could be dimly seen and increase of vision to 12/200. Mild transient secondary glaucoma had developed. The total streptomycin dose was 60 Gm., and that of promizole,® approximately 480 Gm.

CASE 9.—A Negro woman aged 61 was first seen in February 1949. The family and past histories were noncontributory. The present illness was an inflammation of the right eye since August 1948. Examination showed violent sclerokeratitis of the right eye with vision reduced to finger counting at 2 feet. The medical survey showed extensive healed calcified pulmonary tuberculosis and violent hypersensitivity to tuberculin. All other examinations, including biopsy of a lymph node, revealed nothing abnormal. Treatment with streptomycin and promizole® was started Feb. 21, 1949. Promizole® was discontinued on March 22, 1949 on account of toxic symptoms (fever), but streptomycin was continued until April 25. The total dose of streptomycin was 65 Gm., and that of promizole,® 180 Gm. The eye steadily improved, inflammation subsided, the keratic precipitates became crenated, the cornea cleared and vision rose to 20/40 on the patient's discharge, on April 25. On May 24 the eye was entirely inactive and free of all inflammation; vision was 20/20 — 1, and there was one small scar remaining in the cornea.

CASE 10 (presumptive case, referred by Dr. Julius M. Dan).—A white woman aged 24 was first seen March 8, 1949. The family history was noncontributory. The only suggestive finding in the past history was a fistula-in-ano several years previously. Peripheral chorioretinitis developed in the right eye in January 1949; the condition did not yield to penicillin therapy, local treatment or general nonspecific therapy. Examination showed heavy vitreous opacities and some subretinal edema, but no areas of frank exudation. There were numerous Koeppe nodules and heavy mutton fat keratic deposits. Vision was 20/50. The left eye showed keratic precipitates but had 20/20 vision, and no lesions were present in the fundus. Medical survey was noncontributory throughout except for the presence of a calcified nodule in the left lower lung field. The patient was relatively insensitive to tuberculin. A presumptive diagnosis of tuberculous choroiditis was made and the patient placed under therapeutic trial with dihydrostreptomycin and promizole.® This treatment was continued over a forty-two day period, the total dose of streptomycin being 42 Gm. and the dose of promizole® 252 Gm. On June 17, her referring ophthalmologist reported vision of 20/50 in the right eye and 20/20 in the left eye. There were no evidences of any activity on ophthalmoscopic examination. The keratic precipitates either had been absorbed or were crenated. The vitreous opacities were unchanged. Her ophthalmologist summarized his findings as follows: "I feel that the treatment has been of definite benefit. The pathologic process in the eye was progressing up to the time treatment was started. There seems to be a halt in the advancing process."

CASE 11.—A Negro woman aged 24 was admitted to the Johns Hopkins Hospital on March 21, 1949 with a diagnosis of scleritis of the left eye. The family and past histories were noncontributory. Examination revealed that the right eye was negative throughout. The left eye showed a diffuse purplish red congestion, involving all the visible anterior portion of the sclera. There were relative proptosis of the eye and almost complete immobility of the eye. The aqueous ray was present. Vision was 20/20. A diagnosis of deep scleritis, both anterior and posterior, with secondary tenonitis, was made. The medical

survey was essentially noncontributory except for roentgenographic evidences of old pulmonary tuberculosis and moderate sensitivity to tuberculin. She was placed under treatment with streptomycin and promizole® for a period of forty days, and promizole® therapy was continued alone for a further period of twenty-nine days. The total dose of streptomycin was 40 Gm., and that of promizole,® 402 Gm. Notable improvement was noted after fourteen days' treatment. At the end of three weeks the proptosis had disappeared and there was good motility. At the end of the sixth week there remained only slight congestion of the sclera, and at the end of the tenth week there was a complete symptomatic cure, with subsidence of all evidences of scleritis and other inflammation.

CASE 12 (referred by Dr. Luther C. Brawner).—A white woman aged 24 was first seen March 22, 1949. The family history was interesting. Her mother and father had died of tuberculosis, and one brother had active tuberculosis. Her past medical history was essentially noncontributory. She had had repeated attacks of sclerokeratitis in the right eye over a three year period. There had been intermittent tuberculin therapy for three years, with no effect. The left eye had become inflamed one month prior to examination. Examination of her eyes showed pericorneal inflammation of the right eye, with five areas of deep infiltration in the cornea; and ophthalmoscopic examination revealed a small pigmented, atrophic lesion above the macula. Vision was 20/100. The left eye was quiet but showed a paracentral corneal infiltrate and three marginal infiltrates. Vision was 20/15. There were no keratic precipitates in either eye. The medical survey showed violent hypersensitivity to tuberculin (0.001 mg.) and old tuberculous calcification in the left lung and paratracheal area. Treatment with streptomycin and promizole® was begun April 9. She received 1.0 Gm. daily for the first three weeks and thereafter only 0.5 Gm. daily. By May 24 she had taken 32 Gm. of streptomycin without reaction and 252 Gm. of promizole.® Definite clinical improvement was noticed early in May. On May 24 there was a notable lessening of the inflammation, there being only a suggestion of congestion remaining, and the infiltrates were decidedly less. Vision had improved from 20/100 to 20/50. However, four posterior synechias had formed, and there was a nodule-like mass in the stroma of the iris. Both streptomycin and promizole® were therefore continued to July 6, making the total dose of streptomycin 63 Gm. and that of promizole® 504 Gm. On July 6 the patient's physician reported that in the interim there had been temporary vascularization of the cornea, which had regressed. Examination revealed that vision was 20/50; the cornea was clear, except for interstitial scars; there were no keratic deposits, and the aqueous ray was absent. The iris was free of inflammation; there were no nodules. The posterior synechias were still present. There was, however, an area of scleritis at the extreme temporal sclera. Promizole® was discontinued on account of slight anemia and leukopenia. Streptomycin was continued, the dose being increased to 1.0 Gm. a day. This treatment was continued for three weeks. On July 27 all evidences of activity had disappeared and vision had risen to 20/40.

CASE 13.—A white man aged 37 was first seen March 18, 1949. The family and past histories were noncontributory. Retinal hemorrhages had developed in the right eye in 1942, and vision had been reduced in this eye since that date. The left eye was first affected in February 1949. Examination showed bilateral retinal hemorrhages with secondary gliosis, and vision was reduced to 1/200 in the right eye and to 20/70 in the left eye. The medical survey, including biopsy of a lymph node, was noncontributory entirely except for violent hypersensitivity to tuberculin (0.001 mg.) and calcified hilar nodes on roent-

genologic examination. The patient was a veteran and was referred to the Veterans Hospital for streptomycin and promizole® therapy, which was started on April 19. He was given an extremely large dose of streptomycin, 2 Gm. twice daily and 6 Gm. of promizole® daily. Treatment was continued without toxic symptoms up to May 31. The total dose was 168 Gm. of streptomycin and 252 Gm. of promizole.® Examination on June 10, 1949 showed vision of 20/100 in the right eye and of 20/100 in the left eye. The hemorrhage had entirely disappeared. Without further treatment of any kind, the vision on July 12, 1949 was 20/100 in the right eye and 20/40 in the left eye. The right fundus showed a mass of glial tissue extending from the disk and involving the fovea. The left fundus showed a discrete mass of glial tissue between the disk and the fovea, with some secondary granular degeneration of the fovea. There were no hemorrhages in either fundus or any suggestion of activity.

Case 14.—A Negro aged 31 was admitted to the hospital on June 2, 1949, with a history of loss of vision of three weeks' duration. The family and past histories were noncontributory. Examination revealed that vision was reduced to counting fingers in the right eye and to 20/50 in the left eye. The eyes appeared normal to external inspection and examination with slit lamp. Ophthalmoscopic examination showed retinal and vitreous hemorrhages in both eyes, with areas of retinitis proliferans and glial bands extending up into the vitreous. Evidently, the eyes had been the site of repeated hemorrhages for some time, despite the history of onset three weeks previously. The medical survey was entirely noncontributory except for pronounced hypersensitivity to tuberculin and roentgenographic evidence of an old thickened pleura at the base of the right lung. All blood studies gave normal results. Streptomycin and promizole® therapy was started on June 8 and continued for forty-two days, to July 20. There were repeated hemorrhages in the left eye for the first three weeks, and vision decreased from 20/50 to finger counting. Thereafter there were no fresh hemorrhages, and the vitreous cleared steadily in both eyes and the old retinal hemorrhages partially absorbed. On July 9 vision had improved to 12/200 in the right eye and 8/200 in the left eye. On his discharge on July 20, there was no evidence of any hemorrhage, and glial bands were unchanged. Vision had risen to 20/30 in the right eye and 6/200 in the left eye.

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FUNDAMENTAL CONCEPTS IN GLAUCOMA

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THE CONVENTIONAL classification of primary glaucoma which has long been accepted involves a division of its clinical manifestations into two types—simple (or noncongestive) glaucoma and congestive glaucoma. As a general rule the first type develops slowly, quietly and insidiously over many years with a characteristic triad of symptoms—raised tension, typical field defects and cupping of the disk—until in the "absolute" stage the eye becomes intensely hard, all vision is lost and the disk develops a deep, atrophic cup. The second type, on the other hand, is generally characterized by episodic subacute attacks of raised tension, the most notable features of which are the diminution of vision and halos caused by corneal edema; from the less severe of these episodes the eye may seem to recover to a considerable extent, but subsequent attacks tend to involve a permanent raising of the tension (chronic congestive glaucoma) or an acute attack may abolish vision. It is to be noted that the differentiation between the two types is not based on tension, for an eye showing the picture of simple glaucoma may have a tension much higher than one with acute congestive glaucoma. The differentiation depends on the state of the circulation: In the congestive type the primary lesion—at any rate a primary association—is a capillary stasis with increased permeability leading to edema of the tissues of the eye, while in the simple type signs of uveal congestion and edema are absent. To these a third type is sometimes added, forming a subgroup of the simple type; this is characterized by typical glaucomatous changes in the visual fields and atrophic cupping of the disk but without raised tension.

At the meeting of the American Academy of Ophthalmology and Otolaryngology in 1948[1] this classification was "thrown out of the window" as "thoroughly outmoded." In a symposium in which Derrick Vail, Jonas Friedenwald, Peter Kronfeld, Harold Scheie, John Dunnington and Paul Chandler participated, the classification of primary glaucoma into narrow-angled and wide-angled types, proposed by Raeder in 1923, was unanimously and enthusiastically adopted. It is obvious that a collection of opinion and experience so authoritative will

1. Vail; Friedenwald; Kronfeld; Scheie; Dunnington, and Chandler: Symposium on Glaucoma, Tr. Am. Acad. Ophth. & Otolaryng. **53**:169, 1948.

carry an immense amount of weight on both sides of the Atlantic. The purpose of this paper is to inquire whether the suggestion is based on philosophic principles and is an aid to our understanding of that heterogeneous collection of ocular ailments which are characterized by a rise in intraocular pressure or by the symptoms traditionally associated with such a rise.

To a large extent the two systems of classification run parallel. By and large, the cases of narrow-angled glaucoma are congestive in type with an episodic and cumulative clinical history; similarly, the wide-angled type includes most of the cases formerly classified as glaucoma simplex. Based on this single anatomic characteristic, treatment is said to follow in a routine way. In the narrow-angled type surgery is the primary indication—basal iridectomy in cases of acute glaucoma before peripheral anterior synechias develop, iridencleisis after; a filtering operation in cases of the more chronic form. In the wide-angled type operation is advised only when medical treatment has failed, as shown by persistence of a raised tension or a fall in the function of the eye, when a filtering operation should be performed. It would seem that everything depends on raised tension, and that the raised tension itself depends on the width of the angle of the anterior chamber. I wish it were so easy.

From the logical point of view, the matter resolves itself into an inquiry whether the width of the angle of the anterior chamber is in fact the determining factor in the incidence of glaucoma and in the clinical characteristics shown by any particular case. I do not think it is. The immediate (or local) cause of congestive glaucoma is edema of the globe due to uveal vascular congestion. As would be expected from the anatomic layout of the circulation, this congestion particularly affects the ciliary region, and the consequent swelling and edema push forward the root of the iris, narrowing the angle of the anterior chamber until the iris may touch the cornea. If such a condition is marked, and persists, an acute, strangulating attack of glaucoma may ensue; if the engorgement subsides, the swollen tissues may retract, perhaps leaving some peripheral synechias; but if the process is repeated, an ever-increasing number of synechias, depending mainly on the height and duration of the raised pressure, are formed during subsequent attacks, each of which reduces the margin of safety, a chronically raised tension results and the stage is set for a final strangulating attack. It is, of course, obvious that the narrower the angle of the anterior chamber, the sooner such a culmination will ensue; and if the angle is sufficiently wide no acute incident may happen. But the whole of the story is not contained in this apparent blockage of the angle, for, on the one hand, in some 20 per cent of cases of acute congestive glaucoma the angle is found to be open on gonioscopic examination and, on the other, in some cases aqueous humor can be

seen flowing out in the aqueous veins when to all appearances the angle is blocked—a circumstance which becomes more significant when we consider the therapeutic effect of operations designed to establish drainage. The important considerations are that the primary cause of the disease is vascular congestion, that the likelihood of the development of an acute crisis depends largely on the narrowness of the angle, that the synechias which may partially or completely close the angle are the result, not the cause, of the raised tension and that, even in their presence, the drainage of aqueous humor need not be completely suspended.

The effect of surgical treatment in those cases is instructive. Most surgeons are agreed that in the prodromal stage of primary congestive glaucoma a small peripheral iridectomy will usually serve as an efficient prophylactic measure against future attacks. It can hardly be argued that such an operation, leaving a firmly healed cicatrix, can be effective by opening up sufficient drainage channels to insure safety; the more likely explanation seems to be that local axon reflexes determining congestive attacks are in some way inhibited. Similarly, gonioscopic examination of basal iridectomies performed in acute or subacute cases of glaucoma shows that the operation is rarely truly basal. The root of the iris, and sometimes the ciliary processes, are frequently adherent to the corneal wall of the angle; yet in many cases in which the angle seems to have been opened up the tension remains raised, and in as many cases in which the angle remains demonstrably blocked the tension is reduced to normal. While a freely open outlet is undoubtedly a factor never to be despised, and is sometimes of crucial importance in preventing or controlling a future crisis, the effect of the operation is often explained more rationally by a modification of the circulation in the anterior uvea than by a mechanical reopening of wide channels for drainage. Moreover, after an iridencleisis the angle can be shown to have become closed, and a flattened scleroconjunctival scar disproves the persistence of drainage at this point, while the tension remains normal; or, again, after a trephine operation the presence of goniosynechias, or a prolapse of the iris root or the ciliary processes or a flattened, adherent conjunctival flap may be compatible with the maintenance of normal tension, observations suggesting that one factor in the rationale of the operation may be that the operative trauma to the anterior uvea has broken a vicious circle that has determined vascular congestion. In a similar way, the control of the inflammation, and therefore of the congestion, in a case of hypertensive uveitis may result in a reduction of the ocular tension even in the presence of total annular goniosynechias. In all these cases the primary lesion is the vascular congestion; the state or configuration of the angle of the anterior chamber is secondary; clinically, a similar acute crisis may develop with an open or a closed angle, and the tension may well be lowered in the

absence of drainage through the operative cicatrix or be maintained in its presence.

When we consider wide-angled glaucoma, the difficulties increase. Wide-angled glaucoma is not associated with any characteristic depth of chamber, and it may occur in the presence of a wide or a narrow angle; the fact that it would appear to have nothing to do with the dimensions of the anterior chamber or the state of its angle makes it somewhat illogical to define the disease in terms of the angle, but suggests a definition based on the absence of congestion, which is, after all, the essential difference from the other type. So far as my experience is concerned, the angle is normal or wide in about 60 per cent of such cases and narrow in some 40 per cent. Gonioscopy shows that peripheral synechias are rare (occurring in 10 to 15 per cent), discrete, late and incidental. They are, however, frequently seen as the result of postoperative collapse of the anterior chamber.

In the symposium [1] at Chicago, "glaucoma occurring without tension" was stated to be rare (Friedenwald). The relatively common cases of glaucoma which occur in the absence of demonstrably raised tension were said in general to be instances in which a rise in tension occurred intermittently or the height of the tension measured tonometrically was masked by scleral rigidity. With this I find it difficult to agree. I think there are a considerable number of cases characterized by typical glaucomatous cupping, which is frequently very deep and atrophic, and typical slowly progressive glaucomatous field defects but with long retention of the central field, so that, in the absence of complicating raised tension, the disease rarely, if ever, progresses to complete blindness, usually occurring binocularly, but sometimes uniocularly, in persons over 50, and often over 60, most frequently women with a relatively low blood pressure and a low dynamometric reading in the retinal artery—all these signs without any demonstrable rise of ocular tension as taken over periods of years. Sometimes no rise of tension can be demonstrated during periodic visits to the hospital, when several readings are taken each day, or in provocative tests. When the disease occurs uniocularly, the tension in the affected eye may be the same as that in the other, or even somewhat lower; but sometimes (and this, as we shall see, is important) after the lapse of many years the tension may eventually rise, in which case blindness may ensue.

This type of case brings up the importance of the nature and rationale of the cupping of the optic disk. The pathologic picture in such a disk is characterized by early disappearance of the nerve fibers without a reactive increase of glial or connective tissue, so that cavernous lacunas are formed. Such lacunas have been seen in the retina (Schnabel,[2]

2. Schnabel: Arch. f. Augenh. **24**:273, 1892; Ztschr. f. Augenh. **14**:1, 1905; **19**:558, 1908.

Schreiber,[3] Redslob [4]) anterior to the lamina cribrosa, immediately behind it and far up the optic nerve (Behr [5]). A primary and constant accompaniment is vascular sclerosis with disappearance of the capillaries. The whole picture suggests that the changes are typical of what happens to a complex tissue when the blood supply is gradually cut off—the more highly differentiated elements degenerate and disappear without any attempt (owing to the lack of blood supply) at proliferation by the supporting tissues, which, in fact, themselves eventually break down, so that the original small cavities coalesce into large lacunas (Wolff [6]). It is possible that in some cases these vascular changes are secondary to pressure; it is equally possible that in others they are primary. The frequent resistance of the disk to long-standing high pressure in many cases, such as is seen typically with hypertensive iridocyclitis, as compared with the deep cupping so often seen in cases of chronic glaucoma with relatively little (or no) abnormal pressure, would seem to indicate that raised pressure alone is not the sole determinant of the condition. It is probable that the disappearance of the nerve tissue and the weakening of the supporting tissue at and around the lamina may allow the formation of a cup with a normal (or even a subnormal) intraocular pressure. Even in simple glaucoma the depth of the cup bears no constant relation to the tension of the eye.

A note is necessary on the association of cupping of the disks with atrophy and typical glaucomatous field defects sometimes seen in cases with calcified and dilated carotid arteries, a type of case particularly illuminated by Arnold Knapp.[7] Friedenwald accepted the suggestion of Thiel [8] that these changes are the result of pressure on the optic nerve by the calcified artery. The fact that pressure on the nerve by any of the many space-taking lesions that frequently occur in the chiasmal region (aneurysms, pituitary tumors, meningiomas) never produces such changes at the nerve head or in the fields, even though the pressure may eventually involve complete blindness, makes it much more likely that sclerosis of the small vessels of the nerve associated with the sclerosis of their feeding artery is the cause of the lesion, rather than lateral pressure alone.

3. Schreiber: Arch. f. Ophth. **64**:237, 1906.

4. Redslob: Ann. d'ocul. **172**:1, 1935.

5. Behr: Klin. Monatasbl. f. Augenh. **52**:790, 1914; Arch. f. Ophth. **89**:265, 1915; **133**:227, 1937.

6. Wolff: Tr. Ophth. Soc. United Kingdom **68**:133, 1948.

7. Knapp, A.: Association of Sclerosis of the Cerebral Basal Vessels with Optic Atrophy and Cupping: Report of Ten Cases, Arch. Ophth. **8**:637 (Nov.) 1932; Course in Certain Cases of Atrophy of the Optic Nerve with Cupping and Low Tension, ibid. **23**:41 (Jan.) 1940.

8. Thiel: Ber. ü d. Versamml. d. deutsch. ophth. Gesellsch. **48**:133, 1930.

It would seem that in the simple type of glaucoma the factor determining the rise of tension is not the dimensions of the angle, but some subtler obstruction to the drainage of the aqueous humor. This is borne out by the recent evidence of gonioscopy that it is difficult to force blood back from the episcleral veins into Schlemm's canal in established cases of simple glaucoma even if the tension of the eye is normalized by operation or medical treatment. This reverse flow can usually be made to occur readily in the earlier years of life but is seen much more rarely (in less than 40 per cent of cases) in persons over 50 years of age. It would seem that some obstruction to the flow commonly tends to occur with age and that a similar blockage occurs in this type of glaucoma. What the cause of this obstruction in simple glaucoma may be is not known. It is not gonioscopically visible and presumably depends on sclerosis of the exit channels and the trabecular tissue, probably itself secondary to vascular sclerosis in this region; but it is quite clear that it has no relation to the width of the angle of the anterior chamber.

It would seem reasonable to assume that the fundamental pathologic processes occurring in the nerve head and at the angle of the anterior chamber are closely related, if not precisely similar. If the sclerosis affects both areas, there result a cupped disk and raised tension, giving the complete clinical picture of simple glaucoma; if the former alone, there is glaucoma without raised tension; if the latter, there is raised tension with cupping of the disk and field loss as a late and consecutive event. Finally, an increase in tension at a late stage in a case of the "posterior" type is readily explicable by the spread of sclerosis from the posterior to the anterior vessels of the eye. If a term is required to differentiate the occurrence of the process of sclerosis limited to the posterior segment of the eye, "sclerotic optic atrophy" may be found suitable in view of the fact that the connotation of the word "glaucoma" is bound up with the concept of increased tension.

A consideration of the results of treatment of this type of glaucoma is also of importance. Taking simple glaucoma as a whole, my experience shows—and I think it is a fair average—that of eyes in which operative treatment has been adequate and the tension has been brought under control, about 30 per cent do not do well; even of eyes in which the tension has been controlled early, some 15 per cent do badly, and of eyes in which the tension is controlled late, some 50 per cent deteriorate—all despite the persistent and adequate control of tension. It is my impression that if the disease were not one of old age, and patients had a longer average of life after the development of symptoms, this percentage would be considerably higher. I have studied particularly a series of 10 patients all with bilateral typical simple glau-

coma—some with a considerable degree of tension, others with little or none. When tension was present, each eye was trephined and the tension (apparently) normalized; nevertheless, the visual function slowly deteriorated. One eye in each case was subsequently subjected to several operations until the tension was maintained consistently at a subnormal level (about 10 mm. mercury Schiøtz); and in each case the deterioration of function in the two eyes continued to run on in parallel lines. There was no possibility of intermittent rises of tension in the eyes repeatedly operated on. I think the results of all the filtering operations—corneosclerotomy or iridencleisis, or any of their innumerable modifications—give practically identically comparable results; in all of them the tension may well be normalized even if gonioscopy shows the operative channel to be occluded or conjunctival filtration is completely absent. If the be-all and end-all of simple glaucoma were contained in the angle of the anterior chamber and the disease were merely a question of raised tension, there ought to be few functional tragedies in the experience of an enthusiastic surgeon.

Finally, the question of secondary glaucoma should be considered. By "primary" glaucoma we mean a glaucoma the ultimate cause of which is still unknown; by "secondary" glaucoma, those forms due to an established lesion; the former is a concept which will disappear in the future as our knowledge grows. The slit lamp enables us to see minute keratic precipitates, and in a large number of cases glaucoma hitherto known as primary becomes secondary. Senile exfoliation of the lens capsule is discovered, and another batch of cases enters the category of the "known"; Reese [9] described a dystrophic type in which Descemet's membrane and endothelium encroach on the angle of the anterior chamber, and the total of primary glaucomas is again diminished. Any classification of glaucoma should therefore logically include all types.

An issue of this journal dedicated to the life's work and genius of Arnold Knapp is a suitable medium in which I may be sufficiently conservative—or, alternatively, not sufficiently precipitate—to express a preference for the classic classification into *congestive* and *simple* (*noncongestive*) types on the grounds that it is philosophically valuable, since it suggests the fundamental nature of the disease, and is helpful in that it aids in the determination of treatment. Congestive glaucoma is primarily due to vascular imbalance involving congestion, stasis and edema. It may be caused by several factors which are known, such as inflammation, trauma, subluxation of the lens and venous obstruction (secondary glaucomas), or it may be due to vascular crises or instability, the ultimate cause or causes of which are not yet known but

9. Reese, A. B.: Am. J. Ophth. **27**:1193 (Nov.) 1944.

some of which we may surmise may depend on neurohumoral, endocrine, thalamic, psychosomatic or purely local factors (primary glaucoma). In all these cases narrowness of the angle is of importance, since it may bring about an acute crisis by strangulating the ocular circulation; but narrowness of the angle is not causal; it is merely an incident which may affect the course of the disease. Simple glaucoma, on the other hand, is not associated with the picture of vascular congestion. We are very much in the dark as to the cause, and, largely from lack of knowledge of the factors which determine the formation of the intraocular fluid, we have been led to concentrate mainly on the effects of hindrances to its absorption and drainage. Accepting this limitation, we can conclude that the change is mostly of the "anterior" type, acting presumably through obstruction of the drainage of the intraocular fluids (and thus involving raised tension). The obstruction may be due to known factors, such as persistent embryonic tissue (buphthalmos), a growth backward of Descemet's membrane and endothelium, a growth forward of cicatricial tissue from the iris (progressive atrophy of the iris), the deposition and organization of inflammatory material or the deposition of flakes from the lens capsule (secondary glaucomas), or to subtler changes the nature of which we do not yet know but which we suspect are generally of a sclerotic nature (primary simple glaucoma): it is possible that the same type of change confined to the posterior part of the eye may produce corresponding visual changes in the absence of raised tension (sclerotic optic atrophy). In none of these types of glaucoma does the condition of the angle matter, be it wide, normal or narrow. Any type of glaucoma may indeed occur with any type of angle.

I would not give the impression that a rise of tension is a matter of no importance: The reverse is the case, for in its continued presence any eye will probably go blind, and, what is of the highest practical importance, the control of tension is almost the only method of therapeusis available to us in view of our present ignorance of the ultimate cause of many cases of the disease or in view of our inability to influence some of the etiologic factors which we do know. But it is merely a complication—a complication, however, that must be watched with constant and anxious care, that on ocasion may be all-important and catastrophic, or, alternatively, may be merely incidental or even nonexistent—occurring in the course of at least two, and probably more, fundamental maladies. Nor would I decry the undoubted importance of the width of the angle in certain cases, but it is merely an anatomic peculiarity which sometimes influences the gravity of this complication. It seems to me that to make it the central pivot around which the subject of glaucoma hinges is a suggestion lacking in philosophy and full of practical pitfalls.

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SARCOIDOSIS INVOLVING THE ORBIT

Report of Two Cases

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SOME pathologists believe that sarcoidosis is a type of noncaseating tuberculosis, while others maintain that it is a separate disease entity of unknown origin. The similarity of the clinical manifestations of sarcoidosis and tuberculosis and the resemblance of the biopsy findings frequently make the differential diagnosis of these diseases difficult. In cases in which the presence of acid-fast bacilli can be demonstrated, there is no question about the diagnosis; but in the absence of clinical signs of tuberculosis and in cases in which examination fails to disclose Mycobacterium tuberculosis, the biopsy findings may be considered characteristic of either tuberculosis or sarcoidosis.

I shall report 2 cases of sarcoidosis of the orbit which have been observed at the Mayo Clinic.

REPORT OF CASES

CASE 1.—A white woman aged 54, a native of Puerto Rico, came to the Mayo Clinic on Jan. 21, 1926 because of a mass in the left orbit, which she had first noticed in November 1925. The initial symptom had been pain about the left orbit and on the left side of the head. The pain had extended to the left shoulder. Within a few weeks the upper lid had dropped, and she subsequently had been unable to open the left eye. Her previous general condition had been entirely satisfactory.

Vision was 6/7 in the right eye and 6/20 in the left eye. The right eye was normal in appearance, and its functions were unimpaired. In the left orbit a mass could be felt beneath the upper margin. It extended from the area of the supraorbital notch to the temporal rim and along the lower margin to the infraorbital notch. The anterior edge of the tumor, as it appeared on palpation under the orbital rim, was sharp, movable and flexible, but firm. The mass was attached to the temporal border of the orbit. There was moderate chemosis of the lateral half of the globe. The cornea was clear, and the anterior chamber was shallow. The pupil was D shaped, with the curved portion directed temporally. Exophthalmometric readings were 20 mm. for the right eye and 19 mm. for the left eye. Ophthalmoscopic examination did not disclose any abnormality of either eye. Roentgenograms of the orbit were normal. A diagnosis of orbital tumor was made, and operation for its removal was performed on Jan. 27, 1926. The tumor was firm and extended from the region of the supraorbital notch around the temporal wall of the orbit and in the lower lid to the infraorbital notch. It was

removed by blunt dissection. The mass extended into the lower eyelid beneath the skin (fig. 1). It was firmly attached to the skin of the lower lid. The tumor was 1 cm. thick and had a scanty blood supply. It was not encapsulated but was surrounded by loose areolar tissue. Removal of the tumor caused a slight hemorrhage. The external rectus muscle and the lacrimal gland had to be removed with the tumor The pathologic diagnosis was tuberculosis. The patient was dismissed from the clinic on Feb. 24, 1926.

On Feb. 19, 1948, I examined the patient in San Juan, Puerto Rico. The patient was well, and she had not observed any evidence of recurrence of the tumor. Her family physician said that the patient had never shown any evidence of tuberculosis elsewhere than in the orbit.

Original sections of the tumor were reexamined twenty-three years after its removal, and additional sections were cut and examined microscopically. The histologic picture was that of noncaseating tuberculosis, or sarcoidosis. The sections contained numerous tubercles, or nodules, of epithelioid cells associated with a considerable number of multinucleated giant cells and surrounded by a rather scanty infiltration of lymphocytes and plasma cells. A few small areas of degeneration were seen. The tubercles were packed closely in the tissues of the orbit. The lacrimal gland also was involved by the tumor. The involved portion of the lacrimal gland contained fewer nodules of epithelioid cells and a denser infiltration of lymphocytes than the involved portion of the orbit.

Fig. 1 (case 1).—Tumor of the left orbit involving the lower eyelid.

Case 2.—A white woman aged 72, a native of a midwestern state, came to the clinic on Nov. 23, 1948. In August 1948 she had noted a foreign body sensation in her right eye. A short time later the upper lid of the right eye had become swollen. The swelling of the lid had increased gradually, without inflammation or pain. In August 1948 a mass had appeared in the superior temporal quadrant of the right orbit. The mass had increased in size and had caused some exophthalmos and swelling of the lower lid.

Visual acuity, with correction, was 20/30 in each eye. A palpable mass was present in the anterior portion of the right orbit and involved the upper and lower eyelids. It extended deep in the superior temporal quadrant of the orbit. Rotation of the eye was only slightly impaired. On the temporal side, the mass was continuous from the supraorbital notch to the infraorbital notch. Readings obtained with the Hertel exophthalmometer were 17 mm. for the right eye and 15 mm. for the left eye. External examination of the right eye did not disclose any abnormality. The media were clear, and the ocular fundus was normal. The concentration of total protein was 6.1 Gm. per hundred cubic centimeters of serum; the values for the albumin and globulin were 4.2 and 2.0 Gm., respectively, per hundred cubic centimeters of serum. The reaction to the Kline test of the serum was negative. The preoperative diagnosis was orbital tumor, probably adenocarcinoma (fig. 2).

On Dec. 3, 1948 the tumor was removed completely except for a small portion which was situated in the lower eyelid near the external canthus. It was necessary

to remove portions of the levator palpebrae superioris, superior rectus and external rectus muscles which were enmeshed in the tumor. The mass extended into the orbit for a distance of 3 cm. Grossly, it appeared pale and granular.

Fig. 2 (case 2).—Tumor of the right orbit involving the lower eyelid.

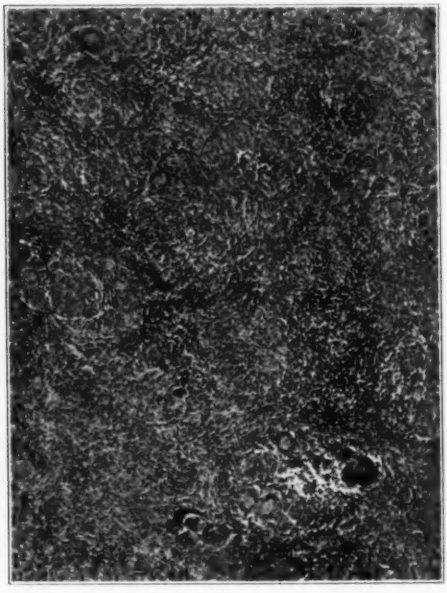

Fig. 3.—Section (× 75) of the mass removed in case 1 in 1926. The diagnosis was tuberculosis. On reexamination in 1948 the resemblance to sarcoidosis was noted.

Microscopic examination revealed that the tumor was composed of many small tubercles, or nodules, consisting of groups or whorls of epithelioid cells, surrounded by fibrous tissue. Fairly numerous large multinucleated giant cells were seen,

chiefly at the periphery of the nodules, although in some of the nodules there was a solitary giant cell at the center. A scanty mantle of lymphocytes surrounded many of the nodules, and occasionally there was a scattering of lymphocytes at the center, sometimes associated with a very small, degenerated-appearing area, but with no evidence of caseation. Many of the larger nodules were irregular in shape and appeared to be conglomerations of smaller nodules. The nodules were invading, and in large part replacing, orbital connective and adipose tissues in the involved area, and to a lesser extent were invading the lacrimal gland. In the lacrimal gland and in other areas near the periphery of the lesion, the lymphocytes appeared relatively more numerous and the nodules of epithelioid cells smaller and scantier. The diagnosis was sarcoidosis (figs. 3 and 4).

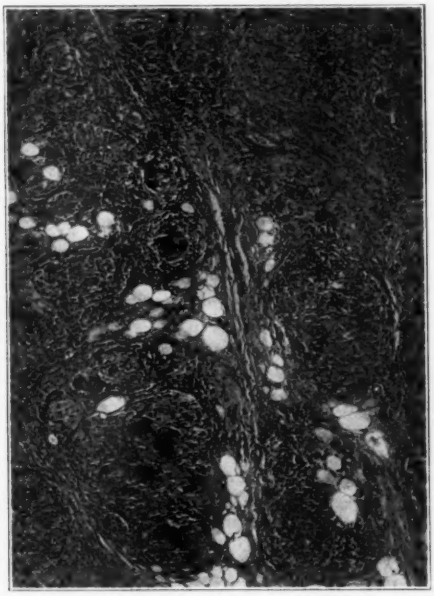

Fig. 4.—Section (× 75) of the mass removed in case 2, in 1948. The diagnosis was sarcoidosis.

After the pathologic diagnosis of sarcoidosis was made, the patient was reexamined for other evidence of the disease, but none was found. She was dismissed from the clinic on December 18.

On Feb. 3, 1949, the patient returned to the clinic because of a recurrence of the tumor in the right lower eyelid. The mass was excised from between the skin and the tarsal plate. A small portion of the skin of the eyelid was involved and had to be removed with the tumor. Bacteriologic examination of the tumor, including the making of cultures, examination of smears and subcutaneous and intraperitoneal inoculation of guinea pigs, did not disclose Myco. tuberculosis. Cultures also failed to disclose Brucella or fungi.

COMMENT

This report is based on 2 cases of sarcoidosis of the orbit which were observed at the clinic in a period of approximately twenty-three years. These 2 cases represent the only instances of sarcoidosis encountered in more than 1,000 cases of tumor of the orbit observed at the clinic. Other cases in which sarcoidosis has been limited to the orbit probably have been reported in the literature, but I have not searched the literature for them. We know that tuberculoma of the orbit is rare. Unless case 1 is considered as a case of tuberculoma, not a single instance of tuberculoma of the orbit has been observed at the clinic. Orbital complications have not occurred in any of the other cases of sarcoidosis which have been observed at the clinic, but intraocular manifestations, such as iritis, chorioretinitis and uveitis, have frequently been present.

The condition known as sarcoidosis is characterized histologically by the presence of a granulomatous, tuberculosis-like lesion which contains epithelioid and multinucleated giant cells but is not associated with caseation necrosis. Some investigators believe that sarcoidosis is a separate disease entity of unknown origin, while others believe that it is a form of noncaseating tuberculosis. Those who believe that it is a separate disease entity usually make the diagnosis by a process of elimination. In cases in which a pathogenic form of Myco. tuberculosis is present, there is no question about the diagnosis of tuberculosis. A diagnosis of sarcoidosis is made in cases in which animal inoculation, bacterial culture and other tests fail to disclose any etiologic agent.

In both the present cases the tumor protruded from the orbital rim within four months after its onset. Both the patients were women who were past middle age. The history was not suggestive of tuberculosis in either case, and laboratory tests in 1 case likewise failed to disclose Myco. tuberculosis. No other sign of tuberculosis or sarcoidosis was found elsewhere in the body in either case.

The gross appearance of the two tumors was similar. Each tumor involved the eyelid beneath the skin. The involvement of the skin was so extensive that the tumor could not be separated. There was no history or sign of external injury which would account for the development of the tumor. The blood supply of the tumors was scanty. The growths were not encapsulated, but they could be separated from the contiguous tissue by blunt dissection.

In case 1, examination did not disclose any evidence of recurrence of the tumor twenty-two years after its removal.

Clinically, the orbital masses in these 2 cases were classified as tumors, although it is not our intention to place them in the category of neoplasms.

The Mayo Clinic.

INVESTIGATION OF VISUAL SPACE

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SINCE January 1948 the chief problem for investigation by the staff of the Knapp Laboratory for Physiological Optics [1] has been the bases on which space perception and spatial orientation are founded. The work is grounded on Luneburg's "Mathematical Analysis of Binocular Vision," [2] which incorporates new and important concepts regarding the fundamentals of space perception, which yields logical and accurate explanations of work already done and facts already known and which promises new possibilities in the experimental and clinical field of vision, with important predictive powers in the fields of art, architecture, industry and war.

THE PROBLEM

Our problem is to discover, evaluate and mathematically express the fundamental, basic relationships between visual stimuli and the sensation they arouse, to find and verify the constant factors operating in this relationship and to seek and describe the underlying constant relationships between binocular stimulus and resultant sensation on which all the subsequent psychologic and experiential factors are added. Psychologically expressed, we are searching for a psychometric coordination. Mathematically expressed, the problem is to find, formulate and, in particular, to verify experimentally a coordination of the sensed points of a visual sensation with the points of a geometric manifold such that the apparent distance of any two sensed points is always proportional to the geometric distance of the correlated points.[3]

This research is being conducted under contract N6onr-27119; project designation no. NR143 638. USN-ONR.

From the Knapp Memorial Laboratories for Physiological Optics, Institute of Ophthalmology, Columbia University College of Physicians and Surgeons.

1. In addition to the author, those working on this project are Dr. Rudolf Luneburg, mathematical consultant; Dr. Paul Boeder, mathematical consultant; Dr. Gertrude Rand, and Miss Catherine Rittler. Since September 1948 Dr. Anna Stein has served as full-time mathematical analyst. Mr. Arnold Kolodny has supplied mechanical assistance.

2. Luneburg, R.: Mathematical Analysis of Binocular Vision, Princeton, N. J., Princeton University Press, 1947.

3. Luneburg,[2] p. 1.

ASSUMPTIONS

The problem is approached by making certain assumptions; checking these assumptions with observation, experimental validification and predictive value and from the mathematical and experimental data thus derived formulating further empiric steps. In such an approach, theory is constantly being modified and redirected by practice, and conversely, the direction and extent of experimentation are daily being changed by the implications of improved or extended theory. Despite ceaseless vigilance, unconscious assumptions (the results of our naïveté, our previous experience, teaching and bias) are likely to enter into our formulation.

The assumption consciously made is that there exists a relationship between physical stimuli and binocular sensation. If we do not accept this, the problem has no meaning. Since we are well aware of the fact that this relationship is not in one-to-one correspondence; that is, the qualities of visual sensation are not uniquely determined by the physical stimuli (the same physical stimulus can arouse different sensations and, conversely, different stimuli can arouse the same sensation), we are forced to conclude that only certain special elements of visual sensation are determined by the stimuli. The essence of the Luneburg theory is that "there exist immutable relationships but that they are confined to the assignments of apparent size to physical line elements." [4] These are the relationships we want to know. They have been formulated mathematically and found to be in perfect agreement with the results of investigations by Helmholtz, Hillebrand, Blumenfeld, Fechner and Ames.

The assumption can be formulated thus: ". . . that the sensations allow recognition of greater and smaller, and of greater and smaller contrast" [5]; that is, that we may compare the sizes of two arbitrary line elements in space even if these line elements are not attached to the same base point. In effect, it presupposes the ability of the observer to make (usually almost instantaneously) a judgment of "greater or smaller and of greater or smaller contrast."

DISCUSSION OF THE PROBLEM

Our visual sense dominates most of our life. Through vision, and particularly through the sensory perceptions aroused by three dimensional binocular vision, our relations to the external world are largely controlled. No other senses reveal nature and the world we live in with such clarity and directness. Color, brightness, form and localization are immediately and vividly sensed through our ocular apparatus. Through our eyes a direct relationship to nature seems to be established.

4. Luneburg,[2] p. 4.
5. Luneburg,[2] p. 6.

That there is a relationship between our visual sensations and the world we live in is assumed as obvious. But how direct is this relationship; how uniform is it, how does it vary in quantitative and qualitative terms; how can it be measured and expressed? These are questions as yet largely unanswered.

"Color," "brightness," "tone" are experienced and thought of as sensations, not as wavelengths, foot lamberts or relative reflectances. They exist in the brain as relative terms, and we know that some persons experience the same stimuli quite differently from others, even though they may be classified as normal observers. "Space," "form," "size," "distance"—these are now included in this category of perceptions which exist in the brain—in our experience—only.

Our sensations are not in one-to-one relationship with the physical counterpart. One unit of physical measurement does not cause 1 unit of perception. Only certain special elements of visual sensation are determined by the stimuli. The brain (perception) adds to a stimulus meaning, significance. Our "sensed" world and the physical world may be similar or not—certainly they are different. How can we show this?

In order to do so, we must differentiate between sensed or "visual space" and "physical space." These two have often been naïvely identified, but this misconception is not permissible.

1. "Physical space" is the measured mappable, blueprint space of the outside world. It is the space in which houses, railroads, bridges and streets are mapped and constructed with great precision. In measuring this space (within small tolerances), all engineers will come out with the same answer. Can we make such measurements in visual space?

2. "Visual space" is the immediate, instantaneous impression we have of our environment as a three dimensional manifold. We have an immediate sensation or impression of objects about us in relative terms: farther, nearer; larger, smaller or equal.

The question immediately arises: What is the relationship between these two spaces, physical space and visual space? Can we find a coordination between the sensed points in visual space and the correlated points in some geometric space such that the apparent distance of any two sensed points is always proportional to the geometric distance of the correlated points?

The entrenched misconception of the identity of the two spaces is the basis of the projection theory of spatial localization, which asserts that a point is sensed at the intersection of the two visual lines. Although useful in some respects, it can be reduced *ad absurdum* on the first attack; e. g., we know that railway tracks, although parallel physically, appear to converge in the distance. This problem has engaged critical minds for

centuries. The physical size of the moon cannot be sensed. A star's distance cannot be sensed. The sky appears not as an infinite space but as a finite, curved dome. These facts break down the projection theory.

On the other hand, the size of the retinal image does not explain these phenomena, because if this were so we would see like a camera, which always shows mountains too small. A man walking away from us retains his apparent size, although the retinal image grows rapidly smaller. This phenomenon is known as "size constancy" in the visual space. It is strongest in our own immediate vicinity. It fails and gradually collapses beyond about 100 meters, the distance depending on the observer.

IMPORTANCE OF THE PROBLEM

The problem is of much more than academic interest. As already noted, it is of potentially great importance in the fields of art, architecture, industry and war. If the metric (the rule, the formula, the measuring rod) of visual space can be formulated, one of the oldest and most interesting problems, the sensory perception of three dimensions by binocular vision will have received considerable clarification. Historically, this would be a great step forward in visual physiology.

In art and architecture, once the metric of visual space is known, the laws of pictorial reproduction can be derived without great difficulty. This would give us a theory of visual perspective quite different from the perspective based on projection from one center. Most certainly, the older technics of vanishing point and central projections would be greatly modified or discarded.

In ophthalmology, knowledge of this metric would yield new insight into all the problems of monocular versus binocular vision; of single binocular vision, fusion, heterophorias and heterotropias; of suppression, stereopsis, ametropia and aniseikonia.

In industry, aside from the architectural implications, one would expect to find important characteristics of groups as a whole (related to plant structure, layouts, stereoscopic representation, safety controls, motion picture technics), as well as of individuals (crane and machine operators, motor drivers, aviators, clerical workers) on which to base plans and selections.

In military and naval practice, a knowledge of the metric of visual space and of the constants characterizing a person in his perception of, and orientation to, objects in physical space would be of great value in the selection and training of personnel. It is for this reason that these investigations at the Knapp Laboratory have for the past year been under the sponsorship and support of the Office of Naval Research.

Every increase in speed of human-controlled carriers calls for a corresponding quickness of orientation and adjustment, and any contribution to the understanding of individual skills and abilities in this field is of great importance. In stereoscopic optical instruments, such as microscopes and range finders, a situation of clueless vision is realized to a considerable degree.

The purpose of these instruments is to determine the physical shape and localization of unknown objects by their apparent shape and localization in a visual space. It is clear that the results can be trusted only if the relation of visual binocular perception to the physical reality is quantitatively known.[6]

BACKGROUND OF THE PROBLEM

Many serious and careful investigations have been made to determine the differences and the relationships between the two spaces "physical" and "visual." I shall here mention only a few of the most important.

1. Helmholtz[7] observed, as before him others had observed, that what seemed to be straight in the horizontal frontal plane was not physically straight. A simple and quickly performed experiment will permit anyone to verify this statement for himself: If, in a darkened room, at eye level, and at about 1 to 2 meters distance, five or more small, dim lights (resembling stars) are arranged in what appears to be a perfectly straight line lying in the frontal plane, this line, when viewed from above, will be found to be not physically straight but markedly curved toward the observer. The amount of curvature will depend on the distance from the observer, the nature of the test objects used and the individual constants or characteristics of the observer. However, for all so-called normal binocular observers, under a given set of experimental conditions (same test objects, same procedures), there will be a range of distances in which the physical curvature is toward the observer (the shorter the distance, the greater the curve); a distance (or narrow range of distances) at which, for a line subtending an angle of 20 to 40 degrees, the apparently straight line *is* physically straight, and, beyond this, a distance at which the apparently straight line is physically convex toward the observer. (With more fun, equal interest and less bother, a similar experiment can be performed in broad daylight. With the subject squatting or lying so that the eyes are near ground level, an assistant arranges five golf balls on a relatively flat lawn or green 20 to 40 feet [6 to 12 meters] away. The balls are to

6. Luneburg, R.: Metric Methods in Binocular Visual Perception Studies and Essays, Courant Anniversary Volume, New York, Interscience Publishers, Inc. 1948, pp. 215-240.

7. Helmholtz, H.: Physiological Optics, Optical Society of America, 1925, vol. 3, p. 318.

be arranged so that they appear to lie in a perfectly straight line at right angles to the line of sight. At this distance the physical curve will probably be convex toward the observer.)

This astonishing fact—that what is visually straight is not physically straight—has been recorded and confirmed many times but has never been explained in terms of basic principles, not even by Helmholtz.

2. These observations led Helmholtz and others to continuations of the experiment. In particular, Hillebrand [8] extended the Helmholtz observations on the frontal plane to walls at right angles to these horopters. The experiments are a little more complicated but just as dramatic and conclusive in their results.

Hillebrand showed that if the test objects (such as vertical strings or wires) were arranged in what appeared to be two perfectly straight and parallel lines (like the walls of an alley), such lines were physically neither straight nor parallel. The curvature changed both with the distance from the observer and with the individual observer (and probably with the type of test object and experimental procedure). Despite these variables, a basic pattern was demonstrable, reproducible and incontrovertible.

3. Blumenfeld [9] repeated, extended and greatly refined Hillebrand's experiment and added an amazing and interesting fact to the store of knowledge already accumulated. Using the same materials, procedures and observers and modifying only one factor in the situation, he produced two different curves which, according to his reports, were consistently and reliably reproducible. Leaving the farthest pair of test objects in exactly the same position, Blumenfeld required his observers, first, to set the other pairs of test objects so that the visual sensation was one of "equidistance"; that is, to the observer the distance between any pair of test objects appeared to be exactly the same as the distance between any other pair—the walls of the alley were "equidistant." These findings having been recorded, the experiment was repeated with nothing changed except the instructions to the observer: The observer was now told to set the test objects so that they would form two straight "parallel" lines, the visual criterion being that of "straightness" and "parallelism"; i. e., no matter how far forward or backward the "straight" walls were projected they would not meet. The "equidistant" and "parallel" curves were not the same. This is a paradox—inexplicable in Euclidean geometry because in Euclidean geometry parallel lines are equidistant. "Equi-

8. Hillebrand, F.: Theorie der scheinbären Grösse bei binocularem Sehen, Denkschriften der mathematisch-natur-wissenschaftlichen Classe der Kaiserlichen Akademie der Wissenschaften, Vienna, 1902, vol. 72, pp. 255-307.

9. Blumenfeld, W.: Untersuchungen über die scheinbäre Grösse im Sehraum, Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. **65**:241-416, 1913.

distant" and "parallel" mean the same thing. This paradox is another hint of different laws operating in the visual space. It is the first clue to the non-Euclidean [10] nature of the visual space.

4. Ames, who studied visual spaces, found other differences between "visual" and "physical" space. His demonstrations of "equivalent configurations" are important and valuable contributions to our growing knowledge of visual space. "Equivalent configurations" supply beautiful and irrefutable evidence that different configurations of physical stimuli can give rise to the same visual sensation. Ames's "distorted rooms" is a superlative example of the difference between "physical" and "visual" space. These rooms are not perspectively related. They have become one of the foundations of a whole new theory of psychology, "perceptionism".[11]

These important basic facts must be considered in any theory of binocular vision or space perception. They can be neither overridden nor dislodged. They militate strongly against utilizing the Euclidean metric in visual space. But they lead also to new and important considerations regarding these two spaces, since, now being freed of the necessity or inclination to consider them as identical, we can inquire separately into the nature of each. This has led to the hope that our problem may be solved and that the relationship of the two spaces can be clarified.

The nature of physical space has been investigated for centuries. Whatever its shortcomings in distances approaching infinity, the Euclidean description of physical space is almost surely adequate in the range wherein human stereopsis functions.

Visual space is demonstrably not Euclidean in its nature. This being so, the question arises: Is there another metric geometry into which we may try to fit the known facts? There are two: the hyperbolic geometry of Bolyai and Lobatschewsky and the elliptic geometry. There are many other non-Euclidean geometries, but only these two maintain the necessary properties of constant curvature, of isotropism and homogeneity. An analytic study of these not only should give valuable information as to which most closely fits observed facts but should yield predictions for further useful experiments.

10. Non-Euclidean is a term used by Gauss to describe a system of geometry different from Euclid's in that the Fifth Postulate regarding parallelism was not used. About 1820, Bolyai, in Hungary, and Lobatschewsky, in Russia, had each developed a non-Euclidean system. Later, Riemann, in Germany, and Cayley, in England, developed another system differing radically from Euclid's. In 1871 Klein classified the various systems, giving the name "parabolic" to the system developed by Euclid, "hyperbolic" to the system developed by Bolyai and Lobatschewsky and "elliptic" to the system of Riemann and Cayley.

11. Cantrill, H.: Understanding Man's Social Behavior: Preliminary Notes, Princeton, N. J., Office of Public Opinion Research, 1947, vol. 7, p. 75.

When the problem is attacked from the other end, important theoretic questions demand attention:

1. Is is possible to find a relationship between the two spaces so that we can go from one to the other?

2. Is it possible to find a coordination between two points in space and the sensation they cause?

3. Is it possible for us to predict what distance sensation will be aroused by two points in physical space?

This task has been attempted by Rudolf Luneburg, who has mathematically analyzed binocular vision with respect to size and distance sensation and has derived the "metric of the visual space"; that is, he has given a means by which we can measure in the visual space. This is, if verified, an important contribution.

What is a "metric"? It is a rule, a ruler, a measuring device, a formula, an equation for measuring distance in a given space. It will vary with different spaces; or, stated more significantly, if the metric is known, all the geometric characteristics of the space are known.

For example, for line geometry the metric is

$$ds \quad \text{(the line element, measured in any units)}$$

for plane geometry the metric is

$$ds^2 = dx^2 + dy^2 \quad \text{(the Pythagorean theorem)}$$

for solid geometry the metric is

$$ds^2 = dx^2 + dy^2 + dz^2 \quad \text{(plane geometry extended to three dimensions)}$$

for spherical trigonometry the metric is

$$ds^2 = d\phi^2 + \cos^2\phi d\theta^2 \quad \text{(The geodesic, shortest distance between two points, is the arc of a great circle.)}$$

A more general metric for three important geometries may be written as:

$$ds^2 = \frac{dx^2 + dy^2 + dz^2}{[1 + \tfrac{1}{4}K(x^2 + y^2 + z^2)]^2}$$

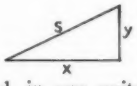
It is immediately apparent that if K (the Riemannian curvature of the space) is equal to 0, the denominator of this equation cancels out and we have the metric given for Euclidean geometry, namely, $ds^2 = dx^2 + dy^2 + dz^2$. In general, this formula fits all three geometries under the following conditions:

$$\text{If } K > 0 \quad \text{(elliptic metric)}$$
$$\text{If } K = 0 \quad \text{(Euclidean metric)}$$
$$\text{If } K < 0 \quad \text{(hyperbolic metric)}$$

The last appears to be the metric of the visual space.

In Euclidean plane geometry, which we have all studied, the metric is

$$ds^2 = dx^2 + dy^2$$



That is ds is the distance to be measured, in any units, between two adjacent points. This metric is the very foundation of plane geometry.

Once we have it, we can derive any theorem—in fact, the whole structure of the geometry. It is the code script of the geometry; just as the gene holds the code script of the man. The whole structure and character of the geometry is determined by the metric; just as the whole structure and character of the man is determined by the gene.

The metric of the visual space is probably non-Euclidean, as was hinted in the discussion of the paradox of Blumenfeld's alley experiment.

We are all familiar with one type of non-Euclidean geometry because we are living on a sphere and two dimensional spherical geometry is non-Euclidean, that is, elliptic. That the spherical geometry is essentially different from the geometry of the Euclidean plane is shown by the fact that it is impossible to make a plane map of the earth without distorting distances. Still, it is possible to study the geometry of the earth with the aid of plane maps if the principle of construction of the maps, that is, the formulas for the distance between any two points, is known. Similarly, the geometry of the visual space can be studied if its "psychometric" is known. Here is the essence of Luneburg's contribution.

The psychometric of the visual space can be expressed, using appropriate binocular coordinates, in the following form:

$$ds^2 = \frac{4}{(e^{\sigma\gamma} + Ke^{-\sigma\gamma})^2}(\sigma^2 d\gamma^2 + d\phi^2 + \cos^2\phi d\theta^2)$$

where K indicates the constant Riemannian curvature of the visual space. This formula establishes a relation between the visual and the physical space. It expresses the general hypothesis that, for an individual observer, the apparent size, ds, of a line element is uniquely determined by its physical coordinates γ, ϕ, θ and by two personal constants σ and K. According to this formula, judgment of visual size is based not only on the angular differentials $d\gamma$, $d\phi$, $d\theta$ but also on the localization, γ, of the line element. The angular differentials $d\gamma$, $d\phi$, $d\theta$ are related to the size of the retinal image. In addition, the factor $\frac{4}{(e^{\sigma\gamma} + Ke^{-\sigma\gamma})^2}$ is related to the sensed size. Our sensed scale of size seems to contract with increasing values of γ, namely, proportionately to the expression $\frac{4}{(e^{\sigma\gamma} + Ke^{-\sigma\gamma})^2}$. Such a well defined contraction can probably be understood only if there is a physiologic basis for it, in the dioptric system of the eyes, on the retina, in the transmission to the brain or in the cortex itself. Luneburg makes no hypothesis concerning this.

That the metric of the visual space is dependent on personal constants is as it should be, for it is suspected that the visual space is different for different persons, and even for the same person at different periods of his life. It is probable that the values of these constants are related to the technical abilities, visual skills and the ametropia of the individual observer.

Luneburg has indicated that there are at least two such personal constants, σ and K, which should be determinable experimentally and which should yield a description of the sensed space of the observer. The constant σ (it may be a function of γ), relates the sensitivity of depth perception to the perception of lateral size, and thus must be related to the interpupillary distance of the observer. Since the threshold of depth perception is considerably smaller than the threshold of size, σ will be considerably greater than 1. The constant K determines the geometric character of the visual space and thus must be considered as a psychologically significant constant which is characteristic for an individual observer. It is of importance for the relation of sensory judgment of size to physical size. Though the two will never be identical, one finds that the best approximation to physical size by sensory estimation is represented by the case $K = -1$. Indeed, in this limiting case, infinite distances are possible in the visual space. Thus, we conclude that the estimation of visual size of an observer agrees with the physical size the nearer to -1 the constant K is found. It is quite possible that a correlation of mechanical abilities to the values of K can be established.

THE THEORY

The theory, then, is that visual space differs from physical space; that if the latter is Euclidean in our vicinity the former is certainly not; that the metric of visual space closely corresponds to, or is identical with, the metric of Lobatschewsky's hyperbolic geometry; that at least two, and probably more, personal constants enter into this metric; that these constants (like refractive errors, aniseikonia, stereopsis, etc.) are fairly stable for a given individual but may be modified by such factors as age, correction of refraction, experience and other factors; that they are probably also closely related to his mechanical and artistic skills, and that they may eventually prove to have considerable predictive value in regard to personnel selection for special tasks.

For devising experiments from the results of which the personal constants σ and K can be determined, there are certain elementary spatial judgments which can be utilized: (1) judgments of relative size and distance; (2) straightness of line, e. g., in a frontal plane or perpendicular to a frontal plane; (3) estimation of right angles or perpendicularity.

A mathematical analysis of the problems and paradoxes previously noted will lead to suggested procedures for determining the values of σ and K for different subjects, as well as indicating whether (as is probable) other constants are involved and what their relative values and importances are. Preliminary work has been carried out in this laboratory on several such procedures, utilizing a comparison of parallel and equidistant alleys, an analysis of certain phenomena observed on Vieth-Mueller circles, quantitative analysis of apparently straight lines in the horizontal plane perpendicular to the median line, the measurements of what appear to be right angles and studies of middistance spaces using plane mirror haploscopes.

It is important to emphasize that this study is merely an approach to the problem of visual space. It is not to be hoped that in a short time all the problems of space perception—including all visual phenomena —will be clarified and solved. It is equally important to note that the approach is new, logical, rational and promising. While I emphatically disclaim any competence to judge the mathematical soundness of Luneburg's derivations, I have taken pains to have them scrutinized by mathematicians of high standing and am assured of their validity. How we apply them, and with what success, lies in the realm of tomorrow.

23 East Seventy-Ninth Street.

SUBCHOROIDAL EXPULSIVE HEMORRHAGE OCCURRING DURING THIOPENTAL SODIUM (SODIUM PENTOTHAL®) ANESTHESIA

Its Treatment by Sclerotomy

DERRICK VAIL, M.D.
CHICAGO

EVERY ophthalmic surgeon, unfortunately, will experience, sooner or later, the occurrence of an expulsive hemorrhage in one or more of his patients after intraocular operation. It is a disastrous complication which probably cannot be foreseen, and for which there is little to be done when it does occur. The one form of treatment that has offered any hope of saving the eyeball at least is prompt incision of the sclera in the area of the hemorrhage and evacuation of the blood.

Posterior sclerotomy for this condition was first performed in 1915 by Verhoeff.[1]

His patient, a man aged 60, had bilateral chronic noninflammatory glaucoma. An iridectomy was performed on the right eye. Almost immediately thereafter vitreous began to pour from the wound. The eye became hard, and there was severe pain. Four hours later Verhoeff performed a sclerotomy to relieve the glaucoma. The first puncture with a Graefe knife was made on the nasal side of the globe, and only a small amount of blood escaped. A second puncture was made on the temporal side, and from this a large quantity of blood flowed and the eye partly collapsed. A third puncture was then made below the second, with the same result. The procedure was then regarded as useless, and the patient was returned to his bed.

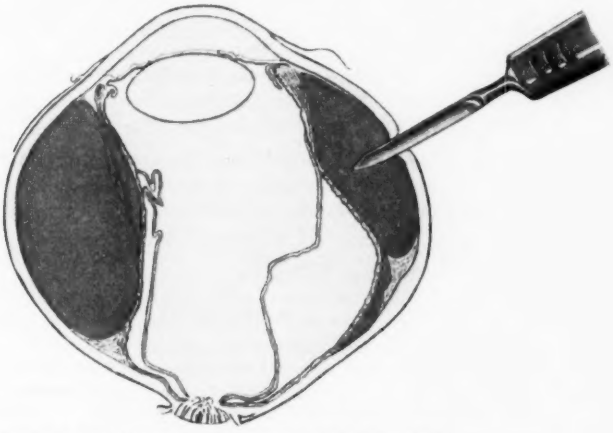
During the night of the following day the pain became severer and a considerable amount of blood flowed from the eye, so that the bandage needed changing. From then on, however, uneventful healing occurred, and three weeks after the operation the vision was 20/200.

In 1937 I reported 2 additional cases in which the eyes were saved and some vision was maintained after posterior sclerotomy for expulsive hemorrage. The first of these hemorrhages followed cataract extraction; the other followed an iridectomy for glaucoma. The details of these cases will be found in the report.[2]

1. Verhoeff, F. H.: Scleral Puncture for Expulsive Sub-Choroidal Hemorrhage Following Sclerostomy, Ophth. Rec. **24**:55, 1915.

2. Vail, D.: Posterior Sclerotomy as a Form of Treatment in Subchoroidal Expulsive Hemorrhage, Tr. Am. Ophth. Soc. **35**:343, 1937; Am. J. Ophth. **21**:256 (March) 1938.

It was pointed out in this paper that the operation of scleral puncture, at the time of the occurrence of the hemorrhage, was most logical and was based on the pathologic condition that was developing. Samuels [3] described this process as a rupture of one of the two long posterior ciliary arteries and expressed the opinion that the seat of the rupture is at the site of entrance of the artery into the perichoroidal space. As the streaming blood drives the choroid forward, other blood vessels at the anterior and posterior aspects of the perichoroidal space may be torn by traction. If the process continues, most of the intraocular content is extruded, even through a very small wound, and the eye is lost. However, the amount of blood may be small and cause only a flat, circumscribed detachment of the uvea far forward. Unless



Sclerotomy for subchoroidal hemorrhage (after Samuels [3]).

there is complete extrusion of the intraocular contents, the blood does not undermine beyond the limits of the perichoroidal space. Samuels stated:

> As this comes to an end posteriorly at a considerable distance from the nerve head, it is exceptional to find blood under the choroid in the posterior segment of the eye. The vortex veins, superiorly and inferiorly fix the choroid to the sclera, in the region of the equator. For this reason, the blood accumulates on the nasal or temporal side, where there is nothing to prevent the choroid from detaching itself from the sclera.[3]

If the hemorrhage ceases and remains confined to the perichoroidal space, a pseudomelanoma results. According to Samuels, localized

3. Samuels, B.: Postoperative Nonexpulsive Subchoroidal Hemorrhage, Arch. Ophth. **6**:840 (Dec.) 1931.

blood remains fluid and unencapsulated for some time. It thus offers an opportunity for drainage by sclerotomy, even in late stages (figure).

Expulsive hemorrhage is ushered in by a sharp, agonizing pain in the eye, accompanied with what Ziegler [4] described as "convulsive or ague-like trembling" of the whole body, associated with a rapid pulse and cold, clammy perspiration. Nausea and vomiting sometimes precede the hemorrhage and at other times follow it.

This hemorrhage usually occurs in the aged person with advanced arteriosclerosis. Hypertensive vascular disease may or may not be present. It has occurred in persons who have not shown any signs of glaucoma. On the other hand, it has not occurred in some elderly arteriosclerotic patients who have had hypermature cataract removed in the presence of acute glaucoma. All observers agree, however, that the rupture of the fragile, arteriosclerotic posterior ciliary vessels is due to the sudden decrease of intraocular pressure following an intraocular operation. Some patients may show little or no generalized arteriosclerosis, with or without vascular hypertension, and yet have arteriosclerotic changes in the long posterior ciliary arteries.

The following case of expulsive hemorrhage, presumably the fourth on record, is described to point out again the value of sclerotomy in this condition, but particularly because the rupture occurred in the course of cataract extraction in a patient under thiopental sodium U. S. P. (pentothal sodium®) anesthesia.

REPORT OF A CASE

A woman aged 69 had a chronic noncongestive glaucoma of the wide angle type, first discovered in 1940. After a trial with miotics, an iridencleisis was performed on the right eye in 1943, with partial success. The ocular tension in each eye was controlled thereafter with miotics. Incipient cataracts were present in both eyes in 1940, and these continued to progress.

At the time she was referred to me for operation, the ocular tension was 25 mm. of mercury (Schiøtz) in the right eye and 18 mm. in the left eye. Vision was reduced to good light projection in the right eye and to 20/50, with correction, in the left eye. The blood pressure was 170 systolic and 80 diastolic, and only moderate arteriosclerosis, compatible with her age, was noted on physical examination, which otherwise showed nothing significant.

On March 7, 1949 it was planned to perform a cataract extraction on the right eye and, simultaneously, an iridencleisis on the left eye. On retrobulbar injection of procaine in the right orbit, a small retrobulbar hemorrhage occurred, producing considerable proptosis of the right eye, so that the operation for cataract was abandoned. An iridencleisis on the left eye was performed without complication, and the eye healed without event. Three days later the proptosis of the right eye

4. Ziegler: The Problem of Choroidal Hemorrhage in Cataract Extraction: Contributions to Ophthalmic Science, Jackson Birthday Volume, Menasha, Wis., George Banta Publishing Company, 1926, p. 7.

had completely receded; ocular movements were normal in all directions, and the ocular tension was 22 mm. of mercury (Schiøtz). It was considered safe to proceed with the cataract extraction.

Because of her nervousness and apprehension, it was decided to perform the operation with the patient under thiopental sodium anesthesia induced by intravenous injection. The blood pressure just prior to anesthesia was 160 systolic and 80 diastolic. It dropped to 130 systolic and 80 diastolic at the beginning of the anesthesia and did not vary, even during the hemorrhage. The pulse rate remained between 90 and 100 a minute.

As soon as the incision with the Graefe knife was made, the wound gaped, and the lens, and then the vitreous, spontaneously began to extrude. On delivery of the lens, the sutures were quickly tied. With focal illumination a small, dark brown elevation, resembling a choroidal melanoma, could be seen in the floor of the eye at 6 o'clock. It increased rapidly in size. A posterior sclerotomy in the area of the choroidal elevation was quickly made and the knife blade held twisted for three or four minutes. During this time a large amount of bright red arterial blood poured from the sclerotomy wound. As soon as the flow slackened, the vitreous protruding between the lips of the sclerocorneal wound was excised and two additional corneoscleral sutures were inserted. The pseudomelanoma was still present, although less in extent, and the eye did not appear hard to palpation. A second sclerotomy to the nasal side of the first incision was performed. Again, bright red blood flowed from the wound, but for a very short time. When it was decided that no further bleeding was taking place, the dressings were applied, and the patient was returned to her room.

During the event, she showed no signs of surgical shock, nor did her blood pressure vary. It remained between 130 and 150 systolic and 80 and 90 diastolic for a few hours after the operation and then gradually reached 175 systolic and 85 diastolic, a level which was considered the average for her. After recovery of consciousness there was no unusual pain and no nausea or vomiting. The patient was entirely comfortable twenty-four hours after operation.

At the time of the first dressing (twenty-four hours after operation) the eye pads were found to be stained with coagulated blood, and the blood clots were washed from the conjunctival sac. There was moderate edema of the lids and conjunctiva. The cornea was clear. Some blood-stained vitreous showed between the lips of the corneal wound, which gaped as far as the sutures permitted it to do. The iris was updrawn, and the pupil was filled with coagulated blood. Light perception was present, but no red reflex could be obtained. The ocular tension appeared low on palpation.

The gaping wound gradually flattened and the eye healed. The patient was discharged thirteen days later.

On examination on May 3, 1949 the corneal reflex was bright and no ocular congestion was present. The pupil was updrawn, and there was a thick membrane in the pupillary space. There was no red reflex. The tension measured 14 mm. of mercury (Schiøtz), and she had good light projection.

COMMENT

The experience in this and in other cases warrants the immediate use of sclerotomy in the event of expulsive hemorrhage. The fact that such a disaster can occur during anesthesia with thiopental sodium should be emphasized. The usual signs of pain and surgical shock are

missing. The surgeon should suspect its occurrence in these circumstances when the lens begins to present as soon as the incision is made, and he should be confirmed in his suspicions when vitreous begins to deliver as soon as the lens is extruded. He should carefully search with oblique illumination, and perhaps with the ophthalmoscope as well, for a "pseudomelanoma" and perform the sclerotomy in this area. It would be better, I think, to make a trephine opening in the sclera and thus allow all blood to escape as long as it will. A knife incision closes rapidly. Verhoeff suggested that small, triangular incisions be made, the apex of the triangle being excised to afford continuous exit to the blood.

It is interesting to note that during the hemorrhage there was no alteration in the patient's blood pressure. Furthermore, the blood pressure was considerably lowered during the anesthesia. This suggests that an elevated blood pressure per se plays no part in the production of this condition. The fact that the patient's left eye had been operated on (iridencleisis) but three days before, without any untoward event, supports the premise that a purely uniocular, local fragility (arteriosclerosis) of the posterior ciliary arteries was present and was responsible for the rupture of the vessels when the intraocular pressure was somewhat abruptly lowered. It is difficult to surmise what role, if any, the previous glaucoma played, for it was bilateral. It was more advanced, however, in the right eye.

It is also difficult to evaluate the part played by the retrobulbar hemorrhage subsequent to injection of procaine three days prior to the cataract operation. I am certain that the retrobulbar pressure had become normal by the time of operation. The proptosis had completely disappeared and the ocular motility had been restored to normal at the time of operation. It is possible, however, that the proptosis of the eye had stretched the sclerotic posterior ciliary arteries, with resultant deleterious effect, and had increased thereby their fragility. However, expulsive hemorrhage has occurred in cases in which retrobulbar injection of procaine has been used without retrobulbar hemorrhage and in the old days before retrobulbar anesthesia was even considered.

From experience in this and in other cases, the logical conclusion is that (*a*) a trephine should be on every cataract instrument tray, (*b*) a sterile trephine or cataract knife should be ready for use on every dressing tray in the event that there is a delayed expulsive hemorrhage and (*c*) every ophthalmic surgeon and resident should be prepared for instant action in the event of a threatened expulsive hemorrhage.

700 North Michigan Avenue.

INTRACAPSULAR EXTRACTION OF CATARACTA COMPLICATA ACCRETA AFTER IRIDOCYCLITIS AND GLAUCOMA

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THE OPERATION for cataracta accreta following iridocyclitis, before the introduction of the intracapsular method by Arnold Knapp, was a source of anxiety to the surgeon and of danger to the patient's eye. Every surgeon who had to operate extracapsularly in cases of this type knows by experience how many eyes were destroyed by the recurrence of iridocyclitis and the hypotony and glaucoma often connected with it. Experienced cataract surgeons, therefore, because of the unfavorable prognosis, declined to undertake extraction in such cases, either on principle, thus condemning the patient to lasting practical blindness, or because they followed the advice of Axenfeld.[1] This author suggested that in such cases one first do a total iridectomy, if it had not already been done, and, with Weber's loop, extract the cataracta complicata as a whole, if possible, so as to save the eye the postoperative recurrence of iridocyclitis caused by remnants of the lens. Therefore, the trauma of loop extraction of the lens used to be the lesser evil in operations on such eyes. I myself can remember, from the days when I was an assistant, many an eye in which the operation was followed by lingering iridocyclitis, occlusion of the pupil, opacity of the vitreous and, occasionally, atrophy of the globe.

If, formerly, surgeons, such as Arnold,[2] Gutmann,[3] Proksch[4] and Seefelder,[5] advocated the extracapsular extraction of cataracta complicata, they thought of this cataract in a broad sense, such as the cataracts following corneal processes, retinitis pigmentosa, detachment of the retina and macular degeneration. Among these, the cataracts following iridocyclitis form the smallest group.

From the First University Eye Clinic.

1. Axenfeld, T.: Die Extraktion nach Iridocyclitis, Deutsche. Ophth. Gesellsch., Heidelberg, 1924.

2. Arnold: Arch. f. Augenh. **25**:41, 1892.

3. Gutmann: Die operative Behandlung der Katarakta complicata, Arch. f. Augenh. **40**: 1900.

4. Proksch, M.: Ueber operative Aussichten bei komplizierter Katarakt, Ztschr. f. Augenh. **92**:129, 1937.

5. Seefelder, R.: Zur Operation des komplizierten Stares, Ztschr. f. Augenh. **57**:12, 1925.

It, therefore, was to the credit of Arnold Knapp to have been the first (in 1910) to recognize the value of intracapsular extraction and to have carried it out systematically. In 1915 Knapp [6] reported on his first 100 intracapsular extractions. His method differed in one essential point from the intracapsular extraction of Stanculeanu, which was published in 1911 and in which the lens was grasped in the middle of the pupil with the forceps and luxated. Knapp, from the very beginning, recommended the grasping of the lens capsule near the lower rim and the tumbling of the lens. This method, modified by Elschnig, was adopted by nearly all ophthalmologists in the following two decades. That A. Knapp originally discarded the Kalt forceps after luxation of the lens and extracted the loosened lens by pressure exerted on the lower portion of the limbus lessens in no way the credit due him. Today, cataract surgeons follow the method proposed by Elschnig and grasp the deep portion of the lens and luxate and tumble it without removing the forceps.

Soon this intracapsular extraction was tried with different kinds of cataracta complicata, and its advantages were recognized. From the historical point of view, one can understand Elschnig [7] when he spoke of the "triumph of the intracapsular method," inasmuch as good results were produced in nearly 100 per cent of cases when this technic was applied to cataracts following cyclitis. Success with the intracapsular extraction of cataract after iridocyclitis was subsequently reported by Arruga,[8] Bonnet and Paufique,[9] Davis,[10] Gaily,[11] Jaeger,[12] Knapp,[13] Krucckmann,[14] Lindner,[15] Passow,[16] Paufique,[17] Sjövall,[18] Sinclair,[19]

6. Knapp, A.: Report of One Hundred Successive Extractions of Cataract in the Capsule after Subluxation with the Capsule Forceps, Arch. Ophth. **44**:1, 1915.

7. Elschnig, A.: Die intrakapsulare Starextraktion, Berlin, Julius Springer, 1932.

8. Arruga, H.: Les advantages et les inconvenients de l'extraction totale de cataracte, Bull. et mém. Soc. franç. opht. **48**:218, 1935.

9. Bonnet, P., and Paufique, L.: Cataracte: La valeur de l'extraction totale, Bull. et mém. Soc. franç. opht. **51**:439, 1938.

10. Davis, F. A.: Personal Experiences with Intracapsular Cataract Extractions, Arch. Ophth. **19**:867 (June) 1938.

11. Gaily, W.: Some Problems Encountered in Cataract Surgery, Am. J. Ophth. **21**:855, 1938.

12. Jaeger, E.: Erfahrungen mit der intrakapsularen Starextraktion, Klin. Monatsbl. f. Augenh. **1**:316, 1940.

13. Knapp, A.: Present State of the Intracapsular Cataract Operation, Arch. Ophth. **38**:1 (July) 1947.

14. Krucckmann, E.: La extracción intracapsular de la catarata, Rev. cubana de oto-neuro-oftal. oftal. **1**:24, 1932.

Wright,[20] Urbanek [21] and others. But the reports did not go beyond general statements, such as, "with cataracta complicata after the iridocyclitis the intracapsular extraction was successful nearly without exception." [15] Horvath,[22] Arruga [23] and Manes [24] referred to the operation for "choroidal cataract," by which they undoubtedly meant cataracta complicata after iridocyclitis.

Contrary to the view of these authors, other surgeons, such as Appleman [25] and Cosmetatos,[26] still advise against intracapsular extraction of cataract with iridocyclitis and either prefer the extracapsular method or refrain from any operation. Moron y Ruiz [27] proposed total iridectomy in cases of cataracta complicata after iridocyclitis, followed by slitting the upper equator of the lens with Graefe's knife and then extraction, one branch of the straight indented forceps being laid into the lens underneath the capsule and the other on the surface of the anterior capsule of the lens, so that the lens is extracted with the capsule. He reported a 10 per cent loss of vitreous in this procedure.

Since the opinions of Elschnig [7] met with opposition in the literature, and since extensive serial examinations are still lacking, I shall report on an unselected series of 105 intracapsular extractions for cataracta

15. Lindner, K.: Ueberblick über die im Jahre 1938 mit meiner geänderten Operationstechnik ausgeführten Staroperationen, Klin. Monatsbl. f. Augenh. **103**: 156, 1939.

16. Passow: Bericht über die intrakapsulare Starextraktion, Klin. Monatsbl. f. Augenh. **100**:764, 1938.

17. Paufique, L.: L'iridectomie préparatoire dans l'extraction capsulo-lenticulaire de la cataracte, Bull. Soc. d'opht. de Paris 1936, p. 115.

18. Sjövall, H.: Starextraktion in der Kapsel, Svenska läk.-tidning **29**:677, 1932.

19. Sinclair, A. H. H.: Presidential Address, Tr. Ophth. Soc. United Kingdom **52**:37, 1933.

20. Wright, R. E.: Lectures on Cataract: IV. Posterior Segment Complications in the Postoperative Period; Some Difficult Extractions, Am. J. Ophth. **20**:376, 1937.

21. Urbanek, J.: Massnahmen zur Verhütung von Komplikationen während und nach der intrakapsularen Starausziehung, Klin. Monatsbl. f. Augenh. **106**:129, 1941.

22. Horvath, B.: Operation einer Flachenhaft angewachsenen Katarakt, Klin. Monatsbl. f. Augenh. **103**:120, 1939.

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complicata accreta after iridocyclitis which were performed in my clinic from 1945 to 1949. My colleagues and I now attempt intracapsular extraction for nearly all kinds of cataracts except those in persons under 30 years of age. Eighty operations of this series were carried out by me personally and 25 by my assistants.

OPERATIVE METHOD

A 5 or 10 per cent solution of cocaine with epinephrine is instilled and akinesis induced with subconjunctival and retrobulbar injection; a traction suture (*Zugelnäht*) is placed through the superior rectus muscle; a "preplaced" suture (Liegard) is used, and then a flap section of over two fifths of the conjunctiva is made with a Graefe knife. Posterior synechias are broken by introduction of a spatula behind the iris as far as the root of the iris with preservation of a round pupil if possible; but if there is an occluding membrane, an extensive total or peripheral iridectomy is first done, so that after detaching the synechias and the pupillary membrane one can grasp the lens in its lower half with the Arruga forceps. If a posterior synechia exists, I first try to make a small peripheral iridectomy at 12 o'clock and then bring the spatula through this opening behind the iris, in order to break the synechia on the posterior surface. In such cases, after the posterior synechia is detached, one should try to perform a total iridectomy or an iridotomy so as to be able to grasp the lens below. If a severe hemorrhage should occur from the vessels of the iris or of the occluding membrane, the operation is interrupted and the intracapsular extraction postponed to a later date. Otherwise, the lens is grasped with the Arruga forceps in its lower half and tumbled or extracted upright under pressure with the spatula at 6 o'clock. Only if the cataract proves to be luxated or subluxated do I grasp the capsule above in the region of the iridectomy, after lifting the iris near the equator above.

The luxation of the lens is usually successfully accomplished by the detaching maneuver with the spatula or as a result of atrophy of the zonule of Zinn due to the cyclitic process. Only when the lens adheres to the anterior limiting membrane of the vitreous body, a condition that is rarely encountered, may the extraction become difficult and vitreous escape. Sometimes a thread of vitreous hangs on the posterior surface of the lens, and this vitreous must be cut off immediately with the deWecker scissors. One, therefore, should always perform the extraction of complicated cataract slowly, while observing every detail minutely.

If extraction takes place with a round pupil, the usual peripheral iridectomy is done. The section removed should not be too small. Then follow the dressing of the wound, the tying of the preplaced suture and the placing of two hair sutures on the temporal and nasal parts of the conjunctival flap.

If the cataract is extracted behind an inflammatory pupillary membrane (occlusio pupillae), a careful vertical section of the occluding membrane may be made with the deWecker scissors or the section of this membrane left until later. Operation is followed by twenty-four hours of rest in bed and bandaging of both eyes; the eye operated on is bandaged for eight days, with daily control, and the patient is dismissed on the twelfth to the fourteenth postoperative day.

As a rule, after such intracapsular extraction, the patient experiences an astonishing absence of irritation of the eye. On the other hand, some eyes with iridocyclitis show after operation a hyphema which is slow to resorb, a Tyndall sign, pronounced traumatic opacity of the cornea or swelling and increase in density of old corneal scars.

In any case, by a successful intracapsular extraction, one saves the eye from the recurrent iridocyclitis which nearly always develops after extracapsular extraction, from dangerous hypotony and from the subsequent discussion of secondary cataract, never without risk to cyclitic eyes.

OBSERVATIONS

The 105 operations for cataracta complicata, to be reported here, were distributed as follows:

Condition	No. of Eyes
Cataracta complicata after iridocyclitis	63
Cataracta complicata after operation for glaucoma with posterior synechias	30
Cataracta traumatica after iridocyclitis traumatica	5
Cataracta complicata with Fuchs's heterochromia	5
Cataracta complicata and aplasia of the iris	2

The formation of synechias was common in the first three groups, in which more or less dense adhesions of the iris to the lens were present. In group 1 the synechias formed after endogenous, usually tuberculous, iridocyclitis; in group 2 the iritis occurred after Elliot's trephination, iridencleisis or iridectomy, and in group 3 the iritis followed a perforating injury. In group 4 cataract followed a lingering uveal disorder (heterochromia), and in group 5, it was superimposed on a congenital inferiority of the uveal tissue (aplasia of the iris). In the last two groups no posterior synechia was noted.

All the patients were examined eight weeks after the cataract extraction, and the majority of the patients also at a later date. The period of observation in the early cases was fifty-four months, and that in recent cases, two months. In a few cases no postoperative examination could be undertaken after the cataract operation. The vision recorded is that which was found at the latest postoperative examination, even when the visual acuity had been better at an earlier examination.

In 16 cases the cataract operation was undertaken on both eyes, and in 73 cases, on only one eye. Among the 89 patients there were 8 one-eyed persons.

Of the 89 patients, 36 were men and 53 women. The age distribution was as follows:

Age, Yr.	No. of Patients
10-19	1
20-29	1
30-39	3
40-49	10
50-59	17
60-69	26
70-79	29
Over 80	2
Total	89

GROUP 1.—*Cataracta Accreta After Iridocyclitis (63 eyes).*—Of these 63 eyes, there were 2 with cataracta complicata after sympathetic ophthalmia, 1 with endogenous hypopyon iritis of unknown cause and 60 with tuberculous iridocyclitis, of which one group showed corneal opacities after phlyctenular keratitis or accompanying tuberculous choroiditis.

The duration of iritis may be summarized as follows:

Duration of Iritis, Yr.	No. of Eyes
1- 9	14
10-19	15
20-29	13
30-42	18
Unknown	2

Of the patients with iritis, 17 were men and 33 women, a total of 50 patients, representing 63 eyes with cataract.

Aspect of the Cataracts: In 61 eyes the cataracts in the posterior cortex were more densely opaque than those in the anterior cortex. Therefore, except for incipient cataracts, they were of the "rosette" type. In 1 eye (with hypopyon iritis) a spotted thickening of the anterior capsule was found; in a second a ring-shaped ridge of the anterior capsule with capsular folds was noted.

Results of Operation: The results of intracapsular cataract extraction for the 63 eyes are tabulated as follows:

No. of Eyes	Result		
51	+	57 eyes, 90.4%	(intracapsular)
3	±		
3	∓		
6	—	6 eyes, 9.6%	(extracapsular)

The sign + indicates that the cataract had been extracted in the capsule without any complication; ±, that the capsule, though it ruptured in a circumscribed spot during the extraction, was nevertheless extracted with the cataract; ∓, that the capsule subsequently could be grasped and removed as a whole, and —, that the lens eventually had to be removed without the capsule. In all cases the final result was complete removal of the lens. This result was confirmed in all cases by examination with the slit lamp.

In 6 cases complications arose during or after the cataract operation. In case 4 a vitreous strand which hung on the posterior surface of the lens had to be cut off with the scissors when the lens was extracted. No loss of vitreous occurred. Vision was 6/8 and ability to read Jaeger's test type 1. In an eye with old sympathetic ophthalmia (case 32) there were loss of vitreous after the section, luxation of the cataract toward the vitreous and, on the fifth day, endophthalmitis, with consequent enucleation. In case 58 serous iritis, probably of allergic nature, developed eight days after the extraction of the cataract (after both operations, serious eczema, resulting from plaster, occurred over the whole face, the neck and the chest), and vision was 6/12 and ability to read Jaeger's test type 1. In case 75, in which at the time of the extraction the lens still showed fresh precipitates, four days after extraction of the lens a slight fibrinous exudation occurred in the anterior chamber. This exudate promptly disappeared after two injections of milk. Final vision was 6/60 and ability to read Jaeger's test type 10, loss of acuity being due to tuberculous retinitis proliferans in the macular region.

In the remaining 57 cases, in spite of the fact that in all cases posterior synechias had to be detached with the spatula, sometimes with hemorrhage into the anterior chamber, the cataract extraction progressed without untoward incidents, and postoperative healing was excellent. It is noteworthy that in 1 case (case 32, old sympathetic ophthalmia) there was loss of vitreous, followed by endophthalmitis, which led to the loss of an eye. In no case was there postoperative prolapse of the iris, because in most cases a broad peripheral or total iridectomy was performed for detachment of the posterior synechia.

Postoperative vision in these 63 eyes was as follows:

Visual Acuity	No. of Eyes
6/6-9/9	17
6/12-6/18	9
6/24-6/36	14
6/60-3/60	7
Less than 3/60	7
Blind	2
No postoperative examination	7
Total	63

The resulting vision appears unfavorable as compared with that after intracapsular operation for senile cataract. This poor result was not the fault of the method of operation but must be attributed to the chronic iridocyclitis with its opacities in the vitreous (often existing for ten to forty years), the complicating tuberculous changes in the eyeground or scars on the cornea, often dating back to childhood, the sequelae of phlyctenular keratitis. Nevertheless, 40 of the 63 eyes had useful vision of 6/6 to 6/36, and only 14 eyes had visual acuity of 6/60 or less. Two eyes were blind.

Of the 14 eyes with vision of less than 6/60, 13 had the cataract extracted in the capsule without complication and 1 had the cataract extracted with the capsule, though the latter was ruptured. This indicates that the poor vision was due not to the operation but to iridocyclitis.

In the 7 cases with vision of 6/60 to 3/60, the causes of the poor function were as follows: opacity of the vitreous with constantly recurring iritis and secondary optic nerve atrophy (case 13); serious chorioretinitis diffusa centralis of long standing (case 16); very dense opacity of the vitreous, obscuring the fundus (case 19); opacity of the vitreous and secondary optic nerve atrophy (case 35); dense opacity of the vitreous, diabetic changes in the eyeground and glaucoma (case 54); contraction of the visual field close to the fixation point following secondary glaucoma (case 60), and central choroiditis combined with corneal opacification (case 103).

Of the 7 eyes with less than 3/60 vision, 6 were of intracapsular extraction without complication, and 1, of rupture of the capsule, with eventual intracapsular delivery, all without complications. The causes of the poor vision were dense opacity of the vitreous and secondary optic nerve atrophy (case 6); corneal opacity, dense opacity of the vitreous and central choroiditis (case 15); disseminated choroiditis and glaucomatous optic atrophy (cases 20 and 21); dense vitreous opacity obscuring the fundus (case 37); diabetic retinitis and vascular hypertension (case 55), and extremely dense opacities of the vitreous caused by consistently recurring iridocyclitis (case 98).

Of the 2 blind eyes, 1 was the eye with sympathetic ophthalmia aforementioned (case 32). In this case, when the cataract was extracted loss of vitreous occurred and a loop extraction was necessary. Subsequently endophthalmitis developed, and the eye was enucleated on the fifth day. The second eye was that of a woman aged 36 with severe tuberculous iridochoroiditis, whose left eye had postoperative vision of 3/36 and ability to read Jaeger's test type 12. Twenty-three months later, because of an unexplained serious hemorrhage in the anterior chamber during pregnancy, the eye became blind, with the signs of xanthomatosis bulbi. The eye had been quiet for twenty-three months following the operation.

Of the 7 eyes not examined after operation, 2 had vision of 6/12 and 6/24, respectively, fourteen days after operation; the other 5 eyes had vision of less than 6/60 because of dense vitreous opacities (2 cases), central choroiditis (1 case), glaucomatous optic nerve atrophy (1 case) and secondary optic nerve atrophy and vitreous opacity (1 case). In 6 of these eyes intracapsular extraction was done without complications (+); in 1 eye the lens was eventually extracted extracapsularly (—).

Summary: Of 63 eyes with moderately severe iritis of from one to forty-two years' duration, the cataracta complicata could be removed by intracapsular extraction in 90.4 per cent (57 cases). In 9.6 per cent the capsule ruptured and the benefit of operation (cataract with sympathetic ophthalmia) was destroyed by endophthalmitis; another eye twenty-three months later was found to have gone blind with the signs of hemorrhagic iridocyclitis, not associated with the cataract operation. In 5 eyes there were slight postoperative complications (hyphema, iridocyclitis). In no case did the iris prolapse. The defect in the final vision attained by the cataract operation is explained in all cases by the preoperative iridocyclitis and its associated complications.

I should like to emphasize that no eye was destroyed by postoperative iridocylitis or hypotony.

GROUP 2.—*Cataracta Accreta After Operations for Glaucoma (30 eyes).*—The posterior synechias which were present in these 30 eyes (27 patients) should be thought of as complications following operations for glaucoma, such as Elliot's trephining, Graefe's iridectomy and iridencleisis. In half the cases there was formation of moderate, and in the other half of extensive and persistent, synechias, all of which had to be detached before the intracapsular extraction.

Of the 27 patients, with 30 cataract extractions, 13 were men and 14 women. The age distribution was as follows:

Age, Yr.	No. of Patients
40-49	1
50-59	2
60-69	9
70-79	14
Over 80	1
Total	27

The distribution of cataract with respect to the type of glaucoma was as follows:

Type of Glaucoma	No. of Eyes
Acute inflammatory	18
Chronic noninflammatory	11
Capsulolenticular	1
Total	30

It must therefore be pointed out that most cataract operations had to be performed on eyes which had previously passed through acute inflammatory glaucoma. In such eyes the tendency to formation of synechia is greater than in eyes with chronic noninflammatory glaucoma.

At the time of the cataract extraction, the glaucoma had dated back as follows:

Duration of Glaucoma, Yr.	No. of Eyes	Duration of Glaucoma	No. of Eyes
½	1	11	2
1	6	12	1
2	6	14	1
3	5	15	2
5	2	17	1
6	1	23	1
8	1		

The cataracts must, for the greater part, be considered as senile, since both the posterior and the anterior cortex were involved. On the other hand, the nuclear cataract, particularly the brunescens type, may be considered as due to glaucoma itself. Furthermore, among these 30 cataractous lenses, 2 were subluxated after trauma, 2 were subluxated after iridectomy and 1 was a milky cataract.

The relation of posterior synechias to operation for glaucoma was as follows:

		No. of Eyes
After one operation for glaucoma		22
After iridencleisis	3	
After iridectomy	14	
After Elliot trephining	3	
After cyclodialysis	2	
After two operations for glaucoma		5
After iridectomy and cyclodialysis	4	
After Elliot trephining and cyclodialysis	1	
After operations for glaucoma		3
After Elliot trephining, iridectomy and cyclodialysis	1	
After Elliot trephining, cyclodialysis and trephining cyclodialysis	1	
After Elliot trephining, cyclodialysis and posterior trephining of the sclera	1	

Results of Operation: In 30 intracapsular cataract operations, which had in every instance been preceded by an ample separation of the posterior synechias by means of the spatula, the results were as follows:

Operation	No. of Eyes	
Intracapsular; no complication (+)	21	25 eyes, 83.33%
Intracapsular; localized rupture but operation completed (±)	2	
Intracapsular; rupture but capsule grasped and reserved as whole (∓)	2	
Operation concluded by extracapsular method (—)	5	16.66%

Thus, the intracapsular operation was successful in 83.33 per cent of the cases; in 16.66 per cent the operation had to be concluded extracapsularly. As in all operations for glaucoma, with the exception of the 2 cases with primary cyclodialysis, a coloboma of the iris was already present, and the spatula could be directed for the detachment of the posterior synechia through the coloboma behind the iris. In a case of ring-shaped synechias after cyclodialysis a total, and in the second case, with slight posterior synechias, a peripheral, iridectomy was done before the detachment of the posterior synechias.

In 2 cases an existing occluding membrane of the pupil was dissected after intracapsular extraction of the lens by means of the deWecker scissors.

Postoperative complications occurred in 3 eyes: In 1 eye (case 22; intracapsular extraction, no complication [+]) slight loss of vitreous and a slight iridodialysis occurred because of dense adhesions of the lens below with the posterior surface of the iris or the ciliary body. Final vision was 6/18 and ability to read Jaeger's test type 2. In 1 eye (case 50) (operation concluded by extracapsular extraction [—]) there was considerable hemorrhage into the anterior chamber. Final vision was 2/60, and inability to read Jaeger's type because of glaucomatous contraction of the visual field beyond the fixation point. In 1 eye (that of a man aged 79, with glaucoma existing for twenty-five years; uncomplicated intracapsular [+] operation) a hyphema developed, followed by chemosis and ingrowth of deep vessels into the cornea from above. Vision six months after the cataract extraction was limited to light perception at 6 meters and good projection. There was a membrane in the coloboma.

A woman of 78 (uncomplicated intracapsular extraction in both eyes) died of cardiac insufficiency five days after the operation on the second eye.

The tension of eyes with glaucoma after the intracapsular cataract extraction remained on the same level as before the operation, that is, within normal limits. In 1 case (case 99) the eye operated on (intracapsular extraction [+]) became soft (10 mm. of mercury), but the vision after three years' observation remained 6/36 with ability to read Jaeger's type 5. In a case in which vision after intracapsular extraction (+) had been 6/18 and ability to read Jaeger's type 2 (case 100), the eye was found to have become blind because of increase of tension when a control examination was made three years later, and this eye was destroyed by a serpiginous ulcer.

In all cases during the cataract section the trephining or iridencleisis scar was taken into account and the filtration scar avoided, the knife being brought forward in front of the scar through the sclera and the cataract incision concluded upward conjunctivally. In this manner it

is possible to avoid changing the appearance and function of a trephining or iridencleisis scar by the cataract incision. For a scar after Graefe's iridectomy I place the cataract incision, if possible, peripheral to the iridectomy scar, so as to reopen the angle of the anterior chamber.

Postoperative vision in 30 eyes was as follows:

Visual Acuity	No. of Eyes	
6/6-6/9	7	22 eyes, 73.33%
6/12-6/18	9	
6/24-6/36	6	
6/60-3/60	0	
Less than 3/60	2	
Hand movements	2	
Blind	1	
No examination	3	
Total	30	

In 73 per cent of the glaucomatous eyes on which intracapsular extraction was performed, the vision obtained was in accord with what could be expected from the glaucomatous field of vision and the changes in the eyeground. In none of these eyes was poor vision the result of the intracapsular extraction; it was due only to the glaucoma.

Of the 2 glaucomatous eyes with less than 3/60 vision after cataract extraction, the glaucoma had existed for twenty-five years in 1 eye (case 50); the lens had been extracted by the extracapsular method (—), and a deep glaucomatous excavation and only a temporal field were present. In the second eye (case 43) glaucoma was of two years' duration, with a history of acute exacerbation (+ extraction) and total glaucomatous excavation.

In the 2 cases with vision limited to perception of hand movements and to light perception at 6 mm., respectively (cases 31 and 63, both with uncomplicated [+] intracapsular extractions of the lens), the poor final vision was due to glaucoma, with optic nerve atrophy, which had lasted for decades.

In the case of blindness (case 100) sight was lost because of continued increase of tension three years after the intracapsular (+) extraction. For 3 eyes (cases 67, 85 and 104) no postoperative examination was made.

In the entire series of 30 intracapsular extraction of cataracta accreta in glaucomatous eyes there was not a case in which vision was favorably influenced by the cataract operation itself.

Summary: Of 30 eyes with glaucoma of long duration and cataracta accreta, the cataract was extracted in the capsule in 83.33 per cent; in 16.66 per cent the operation had to be concluded by the extracapsular method. In all cases the posterior synechias were detached by means of the spatula, which had to be carried out as far back as the root of

the iris. In all cases the final vision was essentially improved by the cataract operation. Poor vision was due to optic nerve atrophy associated with glaucoma. There were no serious complications as a result of the cataract operation in any case. With the exception of 2 cases, tension remained unchanged after the cataract operation; in 1 case there was hypotony of 10 mm. of mercury; in a second case the eye, three years after the intracapsular cataract extraction, was found on postoperative examination to have become blind from glaucoma.

GROUP 3.—*Cataracta Accreta After Iritis Traumatica (5 eyes).*—Again, in cases of cataracta traumatica, before intracapsular extraction can be performed, the posterior synechias must be detached carefully with the spatula. The cataract extraction should take place no less than six months after the perforating injury, i. e., after disappearance of the intraocular inflammation due to the trauma. The 5 cases are summarized as follows:

CASE 10.—Injury of the left eye by the handle of a spade in 1912. Iridocyclitis with posterior synechia and cataracta complicata. Uncomplicated intracapsular cataract extraction (+) in 1945. Final vision with correction 6/6 and ability to read Jaeger 1.

CASE 87.—Extraction of an intraocular foreign body by magnet in 1922. Cataracta traumatica and iridocyclitis. Intracapsular extraction, uncomplicated (+) in 1949; escape of fluid vitreous at the time of incision; luxation of the lens toward the vitreous body after detachment of the synechias. Total iridectomy; extraction by grasping of the lens above. Vision 6/24 and ability to read Jaeger 3. Persistence of the hyaloid artery.

CASE 97.—Injury of the left eye from a piece of wood in 1939; iridocyclitis. Cataracta accreta in 1942. In 1946 intracapsular cataract extraction with peripheral iridectomy (+); excision of thread of the vitreous body hanging from the lens. Final vision with correction 6/8 and ability to read Jaeger 1.

CASE 101.—Injury of the right eye by a splinter of a grenade, in Africa (1943). Adherent leukoma, iridocyclitis and traumatic cataract with crystal formation. Intracapsular cataract extraction (∓) with peripheral iridectomy in 1946. On detachment of the posterior synechia the capsule of the lens was torn in the region of the leukoma. Expression of the cataract and subsequent extraction of the capsule. Vision with correction 6/8 and ability to read Jaeger 1.

CASE 105.—Perforating injury of the left eye by glass with iritis and traumatic cataract in 1927. Anterior and posterior synechias. In 1948 intracapsular extraction with peripheral iridectomy (—): Dissection of the anterior synechia in the anterior chamber; then, during detachment of the posterior synechia, rupture of the capsule, with partial extraction. Final vision with correction 6/18 and ability to read Jaeger 1. Corneal scar.

Of the 5 cases of complicated cataract after performing injury, intracapsular extraction could be done in 4 (uncomplicated [+] in 3 cases and rupture of the capsule with eventual removal [∓] in 1). Vision after the extraction of the cataract was 6/6 in 1 case; 6/8 and

ability to read Jaeger's type 1 in 1 case, because of central cornea scar; 6/8 and ability to read Jaeger's type 1 in 2 cases, and 6/24 and ability to read Jaeger's type 3 in the last case, because of opacities and liquefaction of the vitreous.

The intracapsular extraction, therefore, rendered excellent service in these 5 cases of traumatic cataract.

Group 4.—*Intracapsular Extraction of Cataract with Heterochromia (5 eyes).*—There were 3 men (aged 41, 48 and 18, respectively) and 2 women (aged 58 and 57, respectively) with Fuchs's heterochromia of the iris, precipitates scattered over the entire posterior surface of the cornea and cataract in the lighter eye. In 1 case corneal maculas followed eczematous keratitis. There were no posterior synechias, but diffuse atrophy of the iris was present in 2 cases.

In 4 cases the cataract could easily be extracted intracapsularly (+); in the case of the youngest patient (aged 18) the capsule was so slippery that capsule forceps could not grasp it. The capsule had, therefore, to be torn open with the toothed forceps and the cataract removed extracapsularly. There were no complications in any of the cases.

Vision with correction was 6/6 and ability to read Jaeger's type 1 in 4 cases; in 1 case, because of vitreous opacity, it was 6/18 and ability to read Jaeger's type 2.

It is advisable, therefore, in cases of cataract with heterochromia to use the intracapsular method. It is usually successful in cases of this type. I encountered slippery capsules only in some cases of perinuclear cataract, as in the case mentioned. In these cases an attempt at intracapsular extraction should be made, the lens being grasped by the equator above.

Group 5.—*Intracapsular Extraction in Aplasia of the Iris (2 eyes).*—These 2 cases were included in this paper because these rare cataracts owe their origin to a congenital fault of the uveal tissue. Such cataracts can occur at a comparatively early age.

Case 1.—A woman aged 33 had had reduced vision since her childhood. Operation for cataract was performed on the right eye at the age of 30 and on the left eye in 1945. Escape of liquid vitreous followed the cataract incision. Total iridectomy and intracapsular extraction, uncomplicated (+), were performed. Fourteen days after the extraction vision was 6/24 and ability to read Jaeger's type 4. No postoperative examination was made.

Case 22.—A woman aged 55 had had poor vision since the age of 7 years. Cataract extraction on the left eye in 1934 was followed by choroiditis. Vision was 6/36 and ability to read Jaeger's type 5. In 1946 intracapsular cataract extraction, uncomplicated (+), was performed on the right eye, with subsequent high myopia. Vision with correction was 6/8 and ability to read Jaeger's type 1.

In cases of cataracta complicata of this type the intracapsular method of extraction is indicated because, apparently as a result of the uveal disturbance, the zonule of Zinn degenerates prematurely and the intra-

capsular extraction can be successfully performed at a comparatively early age. In some of these cases, however, one must reckon with complications in the vitreous.

Of the 98 eyes with cataracta complicata in the first three groups, 86, or 87.7 per cent, could be operated on intracapsularly. When Elschnig, in his monograph, spoke of cataracts in cyclitic eyes and mentioned a 100 per cent chance of success, his statement was based only on an impression, not on figures. We must therefore curb our enthusiasm, but we may be confident that in the technic of intracapsular cataract extraction, first practiced by Arnold Knapp, we possess not only a method for the operation of senile cataract, but a procedure that in nearly 88 per cent of cases can be carried out successfully in dealing with cataracts following iridocyclitis. Formerly, it was much more difficult to operate on cataracts of this type, no matter whether the iritis was endogenous or exogenous (due to perforating injury or by operation for glaucoma). Extracapsular cataract operation on such eyes often was followed by a serious recurrence of the iritis or by a return of the glaucoma.

COMMENT

The present series of nearly 100 intracapsular cataract operations for cataracta accreta demonstrates that eyes with such previous severe damage tolerate the intracapsular extraction exceedingly well, that the healing of the wound proceeds smoothly, that the number of complications is not greater than in operations for senile cataract and that in this series of 105 operations the eye was destroyed by an infection in only 1 case. This was the case of sympathetic ophthalmia after perforating injury of the other eye which the patient underwent at an early age. The vitality of the eye was seriously damaged and the infection could not be overcome.

According to A. Knapp and Elschnig, the intracapsular method also makes possible early operation on such cataracts. In eyes with vision already impaired by iritis or glaucoma, operation is especially important, for even the slightest opacity of the lens can blur the remaining vision of such eyes more than would be the case with uncomplicated cataracts. One should, therefore, operate for cataracta complicata with iridocyclitis and glaucoma as soon as possible, intracapsularly. But with all justified optimism, one should always bear in mind those uncertainties which necessarily accompany intracapsular extraction of cataracta accreta.

In spite of careful examination of eyes with iridocyclitis by means of the slit lamp, one cannot see every adhesion between the lens and the iris. Even after most careful separation of the posterior synechias with the spatula, the lens can "hang" when extraction takes place, and it is sometimes very difficult to tumble it or extract it in an upright

position. Pigment deposits which are often found on the periphery of the lens after successful extraction prove the presence of previously unseen synechias which the spatula could not reach. On the other hand, the lens is sometimes actually walled into a cyclitic membrane and can be extracted with surprising ease. Furthermore, one is often surprised at the easy extraction of the lens in an eye with long-standing glaucoma as soon as the posterior synechias have been detached.

Loss of vitreous must always be expected in eyes with uveal disease. Fluid vitreous may escape until the sclera collapses. The resulting sliding back of the lens can on occasion render intracapsular extraction more difficult. As a rule such eyes, after extraction, fill up again within twenty-four hours of their own accord. But loss of vitreous may also be due to adhesion of the lens to the anterior hyaloid membrane. In 2 of my cases, during the extraction a delicate strand of vitreous became visible, which was severed in good time by the assistant and did not lead to any loss.

When in a case of cataract after cyclitis a pupillary membrane exists, the synechias should be detached as usual through a peripheral or a total iridectomy and the lens extracted behind the pupillary membrane. When vitreous does not press forward after the extraction of the lens, one can sever the pupillary membrane and the attached iris at 6 o'clock with deWecker scissors immediately after the extraction of the lens. If the vitreous presses forward into the anterior chamber, one should finish the cataract extraction and undertake iridectomy several weeks later, as otherwise the limiting membrane of the vitreous may easily be incised and vitreous thereby lost.

Nevertheless, the benefit of the intracapsular cataract extraction in such severely damaged eyes is so great that this method, first applied systematically by A. Knapp, marks an important advance in the progress of operative ophthalmology. Poor vision after cataract extraction in eyes with previous iritis or glaucoma is due to opacity of the vitreous, choroiditis, glaucomatous optic nerve atrophy or other complications of the fundus.

EXPERIMENTAL STUDIES ON THE VITREOUS

I. Experiments on Diffusion in the Vitreous and on Permeability of Its Surface Condensation Layer

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CLINICAL experience and scattered experimental data indicate that diffusion in the vitreous is slow.[1] These observations were confirmed in systematic studies of Fischer [2] on diffusion of hemoglobin in arbitrarily divided samples of vitreous and in examinations on spreading of penicillin after intravitreal injection in the living eye.[3] New information on this subject was gained by Kinsey, Grant and Cogan [4] in determining the total movement of vitreous water, with deuterium oxide (heavy water; D_2O) as a tracer substance. The authors concluded from their experiments that the movement of water in the rabbit vitreous was of a magnitude of about 85 cu. mm. per minute. Studies on the eye with radioactive sodium (Na^{24}) autographs [5] provided instructive photographic imprints on diffusion of this normal body constituent in rabbit eyes under physiologic conditions. It was distributed homogeneously throughout the vitreous two to four hours after intraperitoneal injection. The comparison of radio-

This study was supported by the Knapp Memorial Foundation.

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1. Schöler, H.: Ueber das Fluorescein in seiner Bedeutung für die Erforschung des Flüssigskeits-Wechsels im Auge, Verhandlungen der physiologischen Gesellschaft zu Berlin, (February 1882), Arch. f. Anat. u. Physiol., 1882, p. 120. Schöler, H., and Uhthoff, W.: Das Fluorescein in seiner Bedeutung für den Flüssigkeits-Wechsel des Auges, in Schöler, H.: Jahresberichte der (früher Ewers'schen) Augen-Klinik, Berlin, H. Peters, 1881; abstracted, Jahresb. ü. d. Leistung. d. Ophth. **13**:91, 1882. Hamburger, C.: Ueber die Ernährung des Auges, Leipzig, Georg Thieme, 1914.

2. Fischer, F. P.: Ueber die Diffusion von Hämoglobin gegen Kammerwasser, Glaskörper und Blutserum, Arch. f. Augenh. **105**: 431-442, 1932.

3. von Sallmann, L.; Meyer, K., and Di Grandi, J.: Experimental Study on Penicillin Treatment of Ectogenous Infection of Vitreous, Arch. Ophth. **32**: 179-189 (Sept.) 1944.

4. Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, Arch. Ophth. **27**: 242-252 (Feb.) 1942.

5. von Sallmann, L.; Evans, T. C., and Dillon, B.: Studies of the Eye with Radiosodium Autographs, Arch. Ophth. **41**: 611-626 (May) 1949.

graphs obtained from eyes in which radioactive sodium was introduced topically intra vitam or after enucleation gave supporting evidence of a through and through circulation in the animal's vitreous. Radioautographs developed after systemic use of radioactive iodine (I^{131})[6] showed that physical factors other than simple diffusion must be considered in the distribution of sodium iodide in the vitreous. In the experiments reported here, attempts were made to investigate the diffusion of hemoglobin and also of weak and strong acids and bases in the vitreous under various conditions without destroying or disorganizing its architectural structure, and to study the permeability of the condensation layer of the vitreous surface with the same test substances.

DIFFUSION OF HEMOGLOBIN IN THE VITREOUS

TECHNIC

Great care was exercised to avoid or minimize destruction or disarrangement of boundary membranes by applying to fresh pig and steer eyes a technic which was described in a previous paper on the p_H volume curve of the vitreous body.[7] The base of the vitreous and the area Martegiani were protected by leaving the ciliary body and nerve head in place. A ring of sclera and cornea 3 mm. in width supported the preparations when they were suspended in glass jars filled with an isotonic solution of sodium chloride variously buffered to desired p_H ranges. A crystal of thymol was added to the outside fluid to reduce bacterial growth. Thus, the uninjured condensation layer of the vitreous surface was exposed in large windows of the covering coats. Through the openings one could directly observe the movement of hemoglobin, which had been injected with a fine needle (27 gage) either axially or into the more densely packed peripheral region of the vitreous. The solutions of homologous hemoglobin were prepared according to the technic of Fischer.[2] He mixed 2 cc. of 5 per cent sodium citrate with 9 cc. of fresh blood. The red blood cells were centrifuged and resuspended in a 0.9 per cent solution of sodium chloride and again centrifuged. The washing was repeated three times. The washed cells were hemolyzed in distilled water, and the ghosts were removed by centrifugation. The hemoglobin content of the solution was determined in a Sahli hematometer. Pig hemoglobin was used in a 40 per cent concentration; steer hemoglobin, in a 60 per cent concentration. Amounts of 0.1 and 0.15 cc., respectively, were injected into the individual preparations. In experiments on the effect of temperature, groups of 4 to 10 preparations were kept in the refrigerator at 6 C., at room temperature or in the incubator at 37 C. Spreading of hemoglobin either was estimated in fractions of vitreous volume or was determined in linear measure by projecting a millimeter scale at the diffusion zone of the hemoglobin at standard time intervals. Modifications of the technic in other series of experiments will be described in the text.

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6. von Sallmann, L., and Dillon, B.: Studies of the Eye with Radioiodine Autographs, read at a meeting of Association for Research in Ophthalmology in Philadelphia, June 1949, Am. J. Ophth., to be published.

7. von Sallman, L.: Expansion Tendency of the Vitreous and Its p_H Volume Curve, Arch. Ophth. **25**: 243-254 (Feb.) 1941.

EFFECT OF TEMPERATURE AND AUTOLYSIS ON DIFFUSION OF HEMOGLOBIN

Pig Vitreous.—At the start the injected hemoglobin was confined to a small spherical or ovoid area. The depot did not change its size for the first six hours, irrespective of the temperature to which the preparations were exposed. At refrigerator temperature the test substance had diffused within eighteen hours into a portion which was estimated to be about one third or less of the vitreous volume. At a temperature of 37 C., the spreading of hemoglobin involved after eighteen hours at least two thirds of the vitreous, or the entire preparation was stained homogeneously. The results on the specimens kept at room temperature lay about midway between those recorded

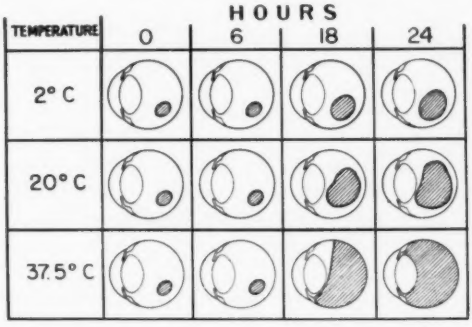

Fig. 1.—Diffusion of hemoglobin in fresh pig vitreous. Shaded areas represent inhibition of vitreous with hemoglobin.

at the two extremes of temperature. Six hours later the stained area was increased to about 60 per cent of the vitreous volume at 6 C., whereas diffusion was complete throughout the colloidal system at the higher temperature ranges. At the forty-eight hour interval autolytic liquefaction of the vitreous was so advanced in preparations kept at 37 C. that this group was discarded. The difference in extent of diffusion between the two remaining groups was still noticeable, as at 6 C. imbibition of the vitreous by hemoglobin was limited to about two thirds of the preparation. In this series the placing of the hemoglobin depot in the looser central portion or in a denser peripheral area of the vitreous did not seem to influence the diffusion gradient. No adsorption phenomena were noticed in the interphases between the fibrillar framework and the liquid content in any of these experiments, which were carried out at a neutral p_H of the outside fluid.

In another series, 36 fresh pig eyes were stored for twenty-four hours at room temperature to induce partial autolysis before injection of the hemoglobin solution. Because pig eyes can be prepared satisfactorily with the described technic only when they are fresh, the hemoglobin was introduced into the intact globes. As in previous experiments, the eyes, in groups of 6, were kept at the three temperature levels for periods of six and eighteen hours. At the termination of the experiment the globes were frozen in a freezing mixture and dissected. At the end of the six hour period the diffusion of the hemoglobin was advanced in all three groups, although at the low tempera-

TABLE 1.—*Effect of Temperature on Diffusion of Hemoglobin in Fresh Steer Vitreous*

Temperature, Degrees (C.)	Number of Preparations	Average Reading, Mm. at					
		0.5	1	2	3	6	20 Hours
6	12	0.9	1.3	1.6	2.0	3.0	5.3
28	12	1.1	1.8	2.5	2.6	3.6	7.6
37	12	1.5	2.1	2.8	3.1	4.9	7.9

ture it did not exceed one-half the vitreous volume. Eighteen hours after injection the hemoglobin had diffused throughout the vitreous in all instances. The difference in the three groups observed at this interval in the previous series was abolished.

TABLE 2.—*Effect of Temperature on Diffusion of Hemoglobin in Partly Autolyzed Steer Vitreous*

Temperature, Degrees (C.)	Number of Preparations	Average Reading, Mm. at					
		1	2	3	4	6	30 Hours
6	11	1.6	2.2	2.8	3.2	4.4	6.8
37	12	1.7	2.4	3.0	3.6	5.1	7.4

Steer Vitreous.—Steer vitreous, with its high turgidity, lent itself better to measurements which could be expressed in millimeters per time unit, as shown in tables 1 and 2. The movement of hemoglobin was considerably slower than in the vitreous of pigs, but a diffusion zone of 1 to 2 mm. was observed as early as thirty minutes after injection at all temperature levels. Since the hemoglobin solution was not made isotonic prior to injection, it must be assumed that osmotic forces were responible for the early spreading. An alternative explanation may be sought in the pressure produced by displaced constituents of the turgid medium. Measurements were then repeated at hourly intervals. Generally the results were in accordance with those described for pig eyes. The zone of diffusion in the preparations kept at 37 C.

was about 1.5 to 1.6 times that measured in vitreous kept at 6 C. The amount of spreading was less consistent in experiments at room temperature, because the latter varied greatly in the summer months.

Partly autolyzed vitreous of steer eyes could be prepared with the technic used for fresh eyes (table 2). The eyes had been kept at room temperature for twenty-four hours before the experiments started. It can be seen in figure 2 that the difference in speed of diffusion under the influence of increments of temperature was strikingly less. As in experiments on pig vitreous, no adsorption phenomena on intra-

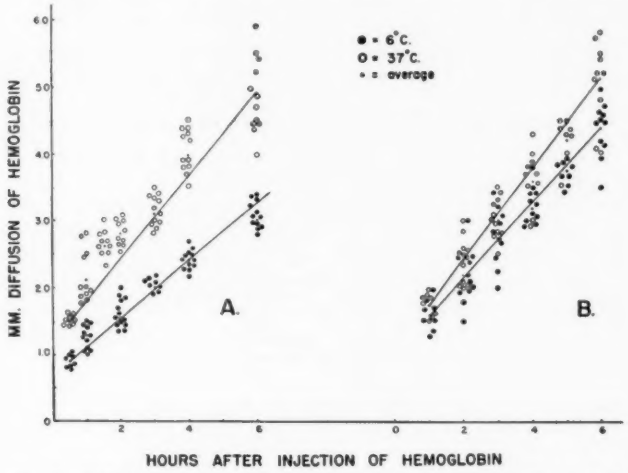

Fig. 2.—Diffusion of hemoglobin in steer vitreous at 6 and 37 C.: (*A*) fresh preparations; (*B*) partly autolyzed preparations.

vitreal phase boundaries were encountered. When hemoglobin was accidentally placed in the hyaloid canal, it filled this potential axial space. Such preparations were excluded from the experiments.

EFFECT OF HYDROGEN ION CONCENTRATION ON DIFFUSION OF HEMOGLOBIN IN STEER VITREOUS

Groups of vitreous preparations like those used in the former series were suspended for twenty-four hours in isotonic solution, buffered to a p_H of 4, 6, 7 and 8. The relatively rapid permeation of hydrogen and hydroxyl ions into the vitreous from the outside fluid was demonstrated in experiments, which will be discussed later. The hydrogen ion concentration of the outside fluid was measured at the end of the experiment and for all practical purposes was found unchanged when

compared with the original values (table 3). The preparations were stored in the refrigerator at 6 C. At p_H 4 the diffusion rate was

TABLE 3.—*Effect of Hydrogen Ion Concentration on Diffusion of Hemoglobin in Steer Vitreous* *

p_H	Number of Preparations	Average Reading, Mm. at			
		1	2	6	18 Hours
4	4	1.6	2.0	3.4	6.9
6	4	1.3	1.8	2.8	5.8
7	4	1.3	1.7	2.8	5.9
8	4	1.4	1.8	2.6	5.8

* Preparations were kept at 6 C.

increased 0.1 to 0.25 time over that obtained in the control experiments at a neutral p_H (fig. 3). Differences of the diffusion zones at p_H 6

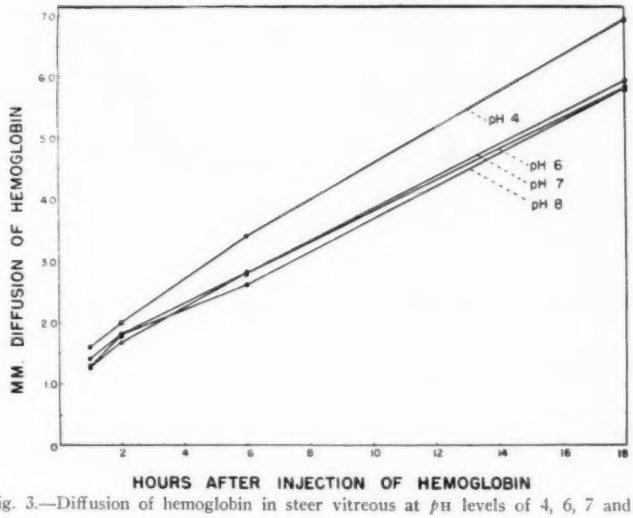

Fig. 3.—Diffusion of hemoglobin in steer vitreous at p_H levels of 4, 6, 7 and 8.

and 8 and at p_H 7 were not significant. No depositions of hemoglobin were seen macroscopically at any of the p_H levels studied.

EFFECT OF THE ENZYME HYALURONIDASE ON DIFFUSION OF HEMOGLOBIN AND NIAGARA BLUE IN FRESH STEER VITREOUS: TENTATIVE EXPERIMENTS

Observations.—With a technic resembling that employed in other series, 60 per cent hemoglobin was injected in 6 vitreous preparations of steer eyes. In 3 preparations hyaluronidase was incorporated in

the hemoglobin solution so that the injected mixture contained 100 depolymerizing units of the enzyme.[8] The preparations were suspended in an isotonic solution of sodium chloride which was buffered to a p_H of 7. Temperatures of 6 and 37 C. were used. In the observation time of twenty-four hours no difference in extent of diffusion was observed between the preparations with the enzyme and the controls.

In a second series, of 12 preparations, a 1 per cent solution of Niagara blue (pontamine sky blue) was used instead of hemoglobin. The experiments were carried out at the three temperature levels, 6, 25 to 30, and 37 C. At refrigerator and room temperatures the preparations with the enzyme showed in a five hour period the same diffusion as the controls. At the incubator temperature (37 C.) small amounts of the dye had diffused partially into the surrounding fluid three and one-half hours after injection of the dye-enzyme mixture, whereas it had not passed the surface membrane of the controls.

Comment.—The effect of temperature on diffusion of homologous hemoglobin in grossly undisturbed fresh preparations of vitreous was in the less turgent pig vitreous greater than in steer vitreous under the same experimental conditions. Although the measurements in the latter were more accurate, they could not be subjected to mathematical analysis. The difference in the vitreous of two species (pig and steer) and the difference in the speed of diffusion between fresh and partly autolyzed preparations pointed to the importance of the structural state of the medium in which the movement of hemoglobin was estimated.

Krause[9] assumed that autolytic disintegration of the vitreous involves, first, peptones, albumins, globulins and the sulfur-containing glucoprotein (mucoid) which was described by Levene.[10] Since this compound was characterized by its gelatinous nature, decrease in turgescence in early stages of autolysis could, according to Krause, be due to the breakdown of the mucoid. Autolytic hydrolysis of the structural proteins seems to follow at a later stage. Meyer and Palmer[11] isolated from the vitreous a sulfur-free, viscous mucopolysaccharide, which they called hyaluronic acid. The authors concluded

8. A potent preparation of hyaluronidase prepared from bull testes was supplied from the laboratory of Dr. Karl Meyer.

9. Krause, A. C.: The Biochemistry of the Eye, Baltimore, Johns Hopkins Press, 1934, p. 176; Wilmer Ophthalmological Institute, Johns Hopkins Hospital and University, Monograph no. 2.

10. Levene, P. A.: Hexosamine and Mucoproteins in Monographs on Biochemistry, London, Longmans, Green & Co., 1925.

11. Meyer, K., and Palmer, J. W.: On Glycoproteins: II. The Polysaccharides of Vitreous Humor and of Umbilical Cord, J. Biol. Chem. **114**: 689-703 (July) 1936.

that this compound was responsible for the turgor and viscosity of the vitreous. The discrepancy between the data of Levene and those of Meyer and Palmer was discussed by the latter authors.[11] In autolysis, depolymerization of hyaluronic acid to a nonviscous form could possibly be brought about by liberation or activation of hyaluronidase from neighboring tissues. The breakdown of the acid might influence liquefaction of the fibrillar network of the vitreous, which is presumably composed of the structural proteins. Recent investigations of Pirie[12] indicated that aggregated hyaluronic acid, as contained in the vitreous jelly, interacts with the structure of the insoluble protein. She concluded from her experiments that "liquefaction of the insoluble proteins was slowed by the presence of the aggregated hyaluronic acid and disaggregation of hyaluronic acid was slowed down by the presence of the insoluble protein." The sequence of changes has not been studied in autolytic liquefaction of the vitreous.

Decrease of viscosity obviously caused in autolyzed preparations more rapid diffusion of hemoglobin. Reduction of frictional forces could be attributed as well to the change of highly polymerized hyaluronic acid to a nonviscous state as to the change in filtering action and adsorption factors which are supposedly functions of the fibrillar structures of the vitreous. However, the diffusion experiments in which the mucolytic enzyme hyaluronidase was added to hemoglobin or dyestuff showed that the jelly of hyaluronic acid was not noticeably liquefied by the enzyme. Similar observations were reported by Blix[13] and by Pirie.[12] These authors did not notice any liquefaction of fresh steer vitreous after use of hyaluronidase. The only exception to the rule in the present experiment was the behavior of Niagara blue in the dye-enzyme mixture at incubator temperature. It seems unlikely, therefore, that depolymerization of hyaluronic acid plays an important part in the initial decrease of viscosity in partially autolyzed vitreous of pig and steer eyes.

The isoelectric point of hemoglobin is at p_H 6.8 to 7. Changes in the p_H of the surrounding fluid to 4, 6 and 8 did not noticeably alter the smooth slope of the diffusion gradient when examined macroscopically and did not lead to macroscopically visible adsorption. One would expect that the ionization and hydration of the hemoglobin molecule at an acid p_H of 4 would produce a decrease in diffusion rate, rather than the increase which was observed in the experiments. It is possible that the diminution in friction of the hydrated molecules or reversible denaturation of the hemoglobin molecule overcompensated

12. Pirie, A.: Ox Vitreous Humor: II. Hyaluronic Acid Relationships, Brit. J. Ophth. **33**: 271-283 (May) 1949.

13. Blix, G.: Some Aspects of the Physiology and Pathology of the Natural Hexosamine and Uronic Acid Compounds, Biochem. J. **40**: 6-7, 1946.

the effect produced by the increase in size due to hydration. The acidity in the vitreous in acute experimental infections did not exceed a p_H of 5.7,[14] so that the rise in the diffusion rate for large molecules in a stronger acid range (p_H 4) has no direct practical applicability.

It is not feasible to compare the data obtained with other test substances (deuterium oxide, radioactive sodium) with those obtained with hemoglobin because the former experiments were carried out on vitreous of low consistency (rabbit). However, among other factors, dependence of the diffusion rate on the molecular size of the used compound cannot be doubted. It was substantiated in the reported experimental series by the speedier movement of Niagara blue as compared with that of hemoglobin in steer vitreous.

EXPERIMENTS ON PERMEABILITY OF THE SURFACE CONDENSATION LAYER OF STEER VITREOUS

PERMEABILITY TO HEMOGLOBIN

Changes in the permeability of the surface membrane of the vitreous have been considered in explaining the mechanism of some forms of secondary glaucoma. The clear therapeutic effect of Chandler's needling operation [15] on the vitreous membrane in certain types of glaucoma in aphakic eyes called immediate attention to disturbances in physical qualities of the surface layer which normally separates the vitreous from the posterior chamber and lens. The following experiments were designed to study the permeability of this structure to the large protein molecule.

Technic: Homologous hemoglobin was mixed with the isotonic solution of sodium chloride in which the vitreous preparations were suspended. A concentration of 0.2 per cent solution was used; the p_H of the solution was buffered to 7. In this series, of 11 preparations, the nerve head and ciliary body were not preserved. In 5 experiments parts of the superficial layers of the vitreous were removed in circumscribed areas. The preparations were placed in the refrigerator, and readings were taken after five, eighteen and twenty-four hours. Finally, after macroscopic inspection, the specimens were frozen in a freezing mixture and bisected. In a second series, of 10 vitreous preparations, a 60 per cent solution of hemoglobin was injected into the vitreous close to its surface to study the penetration from inside outward.

Results.—In the first series of experiments native and frozen preparations showed that hemoglobin penetrated the surface layer of the cortex of the vitreous, but the outermost cover of this layer was macroscopically and biomicroscopically more intensely stained. When, in

14. von Sallmann, L.: Hydrogen Ion Concentration of the Vitreous in the Living Eye, Arch. Ophth. **33:** 32-39 (Jan.) 1945.

15. Chandler, P. A., and Johnson, C. C.: A Neglected Cause of Secondary Glaucoma in Eyes in Which the Lens Is Absent or Subluxated, Arch. Ophth. **37:** 740-771 (June) 1947.

several instances, the posterior capsule of the lens had remained on the anterior face of the vitreous preparation, it also took up more of the hemoglobin. On the other hand, the area Martegiani and arbitrarily produced defects of the superficial layer showed much less tinction by the coloring matter. Penetration of hemoglobin from the evironment into the vitreous substrate extended to a depth of 7 mm. in a twenty-four hour period. In the second series, in preparations kept at refrigerator temperature hemoglobin did not penetrate the surface condensation layer from within for ten hours. The otherwise spherical outline of the diffusion zone was flattened at the surface, corresponding to the contour of the outermost layer. In preparations kept at 37 C. hemoglobin was not completely retained by the condensation membrane at the ten hour interval. A very moderate diffusion through the membrane was noticed even as early as three and one-half hours after injection.

Comment.—The experimental results indicated that the surface layer of the vitreous trapped the large molecule of hemoglobin and offered increased frictional resistance to the passing of hemoglobin inward and outward. These observations suggest that the outer boundary of the vitreous is the seat of a characteristic permeability and that it may be thought of as a semipermeable membrane. This permeability differs from that of the enclosed system and its interphases; here the permeability for hemoglobin was equal throughout, as shown in previous experiments. It is known that physical changes of surface membranes, such as stretching or contraction, can alter their permeability. Such mechanical forces may have been active at the low temperature of the refrigerator and may have added to the effect of the relatively high frictional resistance apparently located in the densely packed mesh of the fibrils of the surface layer. A distinct difference in the behavior of the outer boundary of the vitreous as compared with its bulk was observed by Redslob [16] by treating isolated vitreous preparations with a 5 per cent solution of pyridine. Only the intact surface layer developed a gray opacity. A similar change could be produced with pyridine in dissected human eyes with detachment of the vitreous.[17]

PERMEABILITY TO STRONG AND WEAK ACIDS AND BASES

The penetration of hydrogen and hydroxyl ions into a colloidal system is of great interest. Many studies have been conducted to investigate the relative penetrating power of these ions on plant cells (Elodea,[18]

16. Redslob, E.: Le corps vitré, son dévelopment, sa structure, ses propriétés physicochimiques, Paris, Masson & Cie, 1932.

17. von Sallmann, L.: Zur Anatomie der hinteren Glaskörperabhebung, Arch. f. Ophth. **135**: 593-601, 1936.

18. Harvey, E. N.: Studies on the Permeability of Cells, J. Exper. Zool. **10**: 507-556, 1911.

Spirogyra,[19] Valonia,[20] Nitella,[21] cells of flowers of Rhododendron [22]) and animal cells (Arbacia eggs,[23] starfish eggs,[21b] red blood corpuscles [24]). The technic applied in some of these studies could be modified for use in vitreous preparations.

Technic.—A small amount (0.15 cc.) of an indicator was injected with a fine needle into the central area of isolated preparations of vitreous of steer eyes. A solution of bromthymol blue in a 0.04 per cent concentration or of phenolsulfonphthalein U. S. P. in a 0.02 per cent concentration was used. The solution formed at the start a circumscribed colored area, from which it diffused within a few hours in all directions within the specimen. The preparations were then suspended in about 400 cc. of a 1/400 molar solution of a strong acid or base, i. e., hydrochloric acid and sodium hydroxide, or in solutions of a weak acid or base, namely, acetic acid and ammonium hydroxide. The preparations were kept at 6 C. and observed for six to twelve hours. The speed of penetration was estimated by plotting time against distance measured from the zone where the change in color occurred to the surface of the specimen. Intact vitreous preparations and preparations with arbitrarily produced injuries of the surface layers were compared. Observations were made on 44 vitreous preparations. In an additional series, 16 preparations were first placed at 6 C. in homologous serum for twelve hours and then suspended in the solutions of acids or bases. Fourteen preparations kept in a 0.9 per cent buffered solution of sodium chloride were stored for the same length of time in the refrigerator prior to the transfer of the specimen into the test solutions to serve as controls.

Normal and Injured Vitreous Preparations.—Hydrochloric acid diffused more rapidly than sodium hydroxide. Acetic acid penetrated at a faster rate than ammonium hydroxide. The movement of the weak acid exceeded that of the strong one. The same relation was observed

19. Harvey, E. N.: Relation Between the Rate of Penetration of Marine Tissues by Alkali and the Change in Functional Activity Induced by the Alkali, Washington, D. C., Carnegie Institute, publication no. 183, 1914, vol. 6, pp. 131-146.

20. Brooks, M. M.: Studies on the Permeability of Living and Dead Cells: I. New Quantitative Observations on the Penetration of Acids into Living and Dead Cells, United States Pub. Health Rep. **38:** 1449-1470, 1923; III. The Penetration of Certain Alkalis and Ammonium Salts into Living and Dead Cells, ibid. **38:**2074-2086, 1923.

21. (*a*) Hoagland, D. R., and Davis, A. R.: Further Experiments on the Absorption of Ions by Plants, Including Observations on the Effect of Light, J. Gen. Physiol. **6:** 47-62, 1923. (*b*) McCutcheon, M., and Lucké, B.: The Mechanism of Vital Staining with Basic Dyes, ibid. **6:** 501-507, 1924. (*c*) Irwin, M.: Accumulation of Brilliant Cresyl Blue in the Sap of Living Cells of Nitella in the Presence of NH_3, ibid. **9:** 235-253, 1925.

22. Jacobs, M. H.: The Influence of Ammonium Salts on Cell Reaction, J. Gen. Physiol. **5:** 181-188, 1922.

23. Warburg, O.: Ueber die Oxydationen in lebenden Zellen nach Versuchen am Seeigelei, Ztschr. f. physiol. Chem. **66:**305-340, 1910. Stewart, D. R.: The Permeability of the Arbacia Egg to Ammonium Salts, Biol. Bull. **60:** 171-178, 1931.

24. Jacobs, M. H.: The Permeability of Erythrocytes, Ergebn. Biol. **7:** 1-55, 1931. Jacobs, M. H., and Parpart, A. K.: Is the Erythrocyte Permeable to Hydrogen Ions? Biol. Bull. **62:** 63-73, 1932.

between equimolar solutions of sodium and ammonium hydroxide. Injuries to the surface layers of the vitreous suggested in several instances an increase in penetration rate, but in other preparations no difference was observed between intact and injured parts of the surface.

Preparations Pretreated with Homologous Serum.—The impregnation of the marginal layers of the vitreous with serum protein slowed

TABLE 4.—*Diffusion of a Strong and Weak Acid and a Strong and Weak Base into Fresh Steer Vitreous Suspended in 1/400 Molar Solutions*

Number of Preparations	Acid or Base	Average Reading, Mm. at			
		1	2	3	4 Hours
	A. Intact Preparations				
12*	Sodium hydroxide	2	4	6	12
7	Ammonium hydroxide	4	8	10	14
11*	Hydrochloric acid	4	6	11	14
6	Acetic acid	5.5	9	10	15
	B. Injured Preparations				
4	Sodium hydroxide	2	5	7	11
4	Hydrochloric acid	5	8	14	15

* Including 4 preparations which served as controls in B.

down the diffusion of H^+ from both types of acids. The rate of penetration of bases was less affected by the accumulation of the proteins in the surface zone of the preparation.

Comment.—The more rapid penetration of hydrogen ions through the surface membrane and the speedier diffusion in intact vitreous preparations as compared with hydroxyl ions may have their cause in

TABLE 5.—*Diffusion of Acid and Base into Serum-Soaked Preparations of Steer Vitreous Suspended in 1/400 Molar Solutions*

Number of Preparations	Acid or Base	Average Reading, Mm. at			
		1	2	3	4 Hours
Experimental 4	Sodium hydroxide	3	5	7	10
Controls 3	Sodium hydroxide	3	6	9	14
Experimental 4	Ammonium hydroxide	4	6	9	12
Controls 3	Ammonium hydroxide	5	8	12	15
Experimental 4	Hydrochloric acid	3	5	8	10
Controls 4	Hydrochloric acid	6	11	15	..
Experimental 4	Acetic acid	4	6	9	11
Controls 4	Acetic acid	6	11	15	..

the smaller size of the former or in differences in changes in the diffusion medium produced by acids and bases. Molecules have the property of penetrating colloidal systems relatively faster than ions. The rate of penetration depends, therefore, on the dissociation constant of the substance studied. As in experiments on plant cells and animal cells, weak acids and bases entered the vitreous at a faster rate. Rapid diffusion of NH_4 and the subsequent change in the p_H in the steer vitreous were in agreement with numerous observations made in experimental biology.

Results in preparations of normal vitreous with injured surface layers suggested in the majority of experiments a moderate increase of penetrability for the acids and bases used, but this observation was not confirmed in other instances. In these experiments it was not possible, therefore, to demonstrate an unquestionable difference in the permeability between the outer boundary and the enclosed system as it was indicated in the studies with hemoglobin. The impregnation of peripheral layers of the vitreous with serum proteins delayed the onset of the changes in the p_H in the more central portion of the vitreous. The most likely explanation of this phenomenon may be seen in increase of buffering capacity in the surface zone of the vitreous due to accumulation of serum protein. Blocking of the pore system of the membrane sieve with increased frictional resistance represents another mechanism which must be considered. The surface layers of the preparation which had been pretreated with serum developed in the acid environment a gray, dense precipitation film. This physicochemical change may have impeded the movement of the test substances in later stages of the experiment.

SUMMARY

1. The diffusion rate of homologous hemoglobin in undamaged vitreous preparations was increased by temperature increments and by autolytic decomposition of the colloidal system. These influences were greater in pig than in steer vitreous.

2. In general, mixtures of hemoglobin or Niagara blue with hyaluronidase preparations did not diffuse more rapidly in steer vitreous than did hemoglobin or the dye alone.

3. At p_H ranges of from 6 to 8 changes in the hydrogen ion concentration of the milieu did not noticeably influence the character or rate of diffusion of hemoglobin in the steer vitreous.

4. The surface condensation layer of the vitreous differs in its permeability for hemoglobin from the permeability of the enclosed system and its boundary interphases.

5. Hydrochloric acid penetrated the surface layer and diffused at a higher rate in the vitreous than did sodium hydroxide. Similarly, acetic acid moved faster than ammonium hydroxide. The diffusion rate of the weak acid and base exceeded that of the strong acid and base.

6. No distinct difference in permeability for hydrogen ions and hydroxyl ions was demonstrated between the surface membrane and the bulk of the vitreous body.

7. Impregnation of the peripheral vitreous layers with serum proteins slowed the penetration of acids and, to a lesser degree, that of bases.

Dr. Karl Meyer supplied me with the enzyme preparations. Miss J. Di Grandi and Miss B. Dillon assisted in this study.

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CATARACT FORMATION IN THE HUMAN EMBRYO AFTER RUBELLA

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BILATERAL cataract formation in an 11 week embryo with a history of rubella in the mother during the eighth week of pregnancy is of sufficient interest to warrant publication.

Reese [1] (1944) recorded the first observation in the United States of congenital cataract formation in infants born of mothers who had rubella in the early part of pregnancy. The original description of this condition was made by Gregg [2] and by Swan and his co-workers.[3] An epidemic of rubella in Australia aroused their attention to the prevalence of this condition. Since the aforementioned reports, many cases have been recorded, so that the process is now well recognized. Besides cataract formation, the infants have other defects: intolerance to atropine; inability to dilate the pupil; a high incidence of susceptibility to pneumonia, with high fever; mental deficiency, and microcephaly. Deaf-mutism has also been reported fairly frequently. The children are small, ill nourished and difficult to feed.

The cataractous lens shows involvement of all but the outermost layers, and the cataract is considered to have developed early in embryonic life. Though the condition is usually bilateral, monocular involvement has been reported. Nystagmus, strabismus, corneal opacities, microphthalmos and glaucoma have also been observed.

Since publication of the studies by Swan and Tostevin,[4] the first three months are conceded to be the critical period of pregnancy for the development of congenital abnormalities resulting from rubella.

From the Francis I. Proctor Foundation for Research, Division of Ophthalmology of the University of California.

1. Reese, A. B.: Congenital Cataract and Other Anomalies Following German Measles in the Mother, Am. J. Ophth. **27**:483 (May) 1944.

2. Gregg, N. M.: Congenital Cataract Following German Measles in Mother, Tr. Ophth. Soc. Australia **3**:35, 1942.

3. Swan, C.; Tostevin, A. L.; Moore, B.; Mayo, H., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, M. J. Australia **2**:201 (Sept.) 1943.

4. Swan, C., and Tostevin, A. L.: Congenital Abnormalities in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella: A Third Series of Cases, M. J. Australia **1**:645 (May) 1946.

So far as involvement of the lens is concerned, this has been verified, since no cases of cataract have been reported in which rubella was contracted after the third month. Substantiation of the belief that changes do occur in the lens during the first trimester has been very limited. The number of embryos obtained for study from women having rubella during the first trimester has been very small.

Swan [5] described the first embryo in 1944. A 2½ month embryo was obtained from a woman who had had rubella late in the second month of pregnancy. Examination disclosed considerable disorganization of the structures of the right eye, including microphthalmos, cataract formation and failure of closure of the fetal fissure. The blood vessels supplying the lens were reduced in number. The left eye failed to show any abnormality. In this embryo, then, there were definite abnormalities, which included actual cataract formation in one eye, while the other eye was normal. This occurrence coincides with clinical observations that in some children cataract formation may develop in only one eye.

The second case was reported by Cordes and Barber [6] in 1946. The specimen consisted of an embryonic eye recovered after a therapeutic abortion, terminating a pregnancy of eight weeks. There was a history of rubella in the mother during the fifth week. Microscopic examination revealed that the optic cup was well formed and the outer layer fully pigmented. The outer and inner walls of the optic cup had become approximated, and the fetal fissure had closed. The hyaloid system was fully developed, and the hyaloid artery contained blood. The cells of the posterior portion of the retina had differentiated into the inner and outer neuroblastic layers. Mesodermal tissue covered the anterior surface of the lens, but the anterior chamber had not formed. The anterior portion of the tunica vasculosa lentis was poorly defined, but the lateral and posterior portions appeared normal. The subcapsular epithelium of the lens showed distortion and disorientation of the cells at the anterior pole. The primary fibers had elongated but did not completely fill the cavity of the lens vesicle. The fibers were swollen and stained poorly, appearing vacuolated at their anterior ends. The nuclei also stained unevenly. The lens capsule was difficult to trace. The lens showed definite retardation of development and differentiation, while the posterior segment was normal. Terry compared the specimen with those in the Minot Embryological Collection at Harvard University and stated that the lens showed the differentiation and size of a 17 mm.

5. Swan, C.: Congenital Malformations in Infants Following Maternal Rubella During Pregnancy: A Review of Investigations Carried Out in South Australia, Tr. Ophth. Soc. Australia **4**:132, 1944.

6. Cordes, F. C., and Barber, A.: Changes in Lens of Embryo After Rubella, Arch. Ophth. **36**:135 (Aug.) 1946.

embryo, while the differentiation and over-all size of the eye corresponded to the 19 mm. stage. This retardation of the development of the lens was confirmed by Ida Mann when she saw the specimen.

In 1948 Helweg-Larsen, and Nielsen[7] of the University Institute for Human Genetics of Copenhagen, reported on the study of a 25 mm. embryo obtained after the mother had had rubella. The lens was underdeveloped, and the lens fibers did not fill the lens cavity and also showed fine vacuolation. They suggested that more young embryos from women who contracted rubella during pregnancy be studied, possibly with the aid of analysis of the ultraviolet absorption spectrum, to determine disturbances in the cell protein metabolism, which is influenced early by virus infections.

REPORT ON FOUR EMBRYOS

SPECIMEN 1.—In the early part of 1948, two embryonic eyes were received by us at the Proctor Laboratory of the Division of Ophthalmology of the University of California. Dr. James Harkins and Dr. Melvin Friedman, of the Permanente Foundation Hospital, Oakland, Calif., permitted us to present the results of study.

History.—The mother had rubella during the second month of pregnancy, and a therapeutic abortion was performed at the 11 week stage.

The head had been removed from the body and the eyes dissected from the orbit and fixed in dilute solution of formaldehyde U. S. P.

RIGHT EYE

Gross Examination.—The specimen measured 5 by 4 by 4 mm. Some tissue adhered to the cornea. The lens appeared dense white and opaque. The anterior chamber was very shallow, and the cornea was clear. The margin of the optic vesicle lay at about the equator of the lens.

Microscopic Examination.—The specimen appeared to be well fixed, as the epithelium of the eyelids and of the cornea was intact. The retina showed only very slight postmortem degeneration (fig. 1).

Cornea.—The corneal epithelium had undergone slight surface desquamation, and some of the central cells were completely missing. This may have occurred at the time of removal of the eye. Bowman's membrane (lamina elastica anterior) was not seen. The stroma had a uniform thickness and contained a large number of cells, a developmental stage characteristic of a fetus of the age of this specimen. Descemet's membrane (lamina elastica posterior) was not yet present. The endothelium was intact.

Limbus.—The anterior vascular network of the sclera was rudimentary, and the definitive trabecular meshwork was not present. Schlemm's canal was not seen.

Anterior Chamber.—The whole anterior chamber was extremely shallow, owing to the large size of the lens. The angle was rounded and filled with mesodermal tissue.

Iris.—The pupillary portion of the tunica vasculosa lentis was present. The mesodermal portion of the iris extended a short distance centrally along the anterior capsule, but the epithelial layers lay just anterior to the equator of the lens.

7. Helweg-Larsen, and Nielsen, E. L.: Forändringer i fosterlinse efter rubeolae? Ugesk. f. læger, 1948, no. 49, p. 1394.

Ciliary Body.—There was very slight early differentiation of the corona with some folding of the epithelial layers. The stroma was poorly defined, and the ciliary muscle showed only slight differentiation.

Choroid.—Bruch's membrane (lamina basalis) was not present, and there were very loose layers of small blood vessels in the mesoderm of the choroidal stroma.

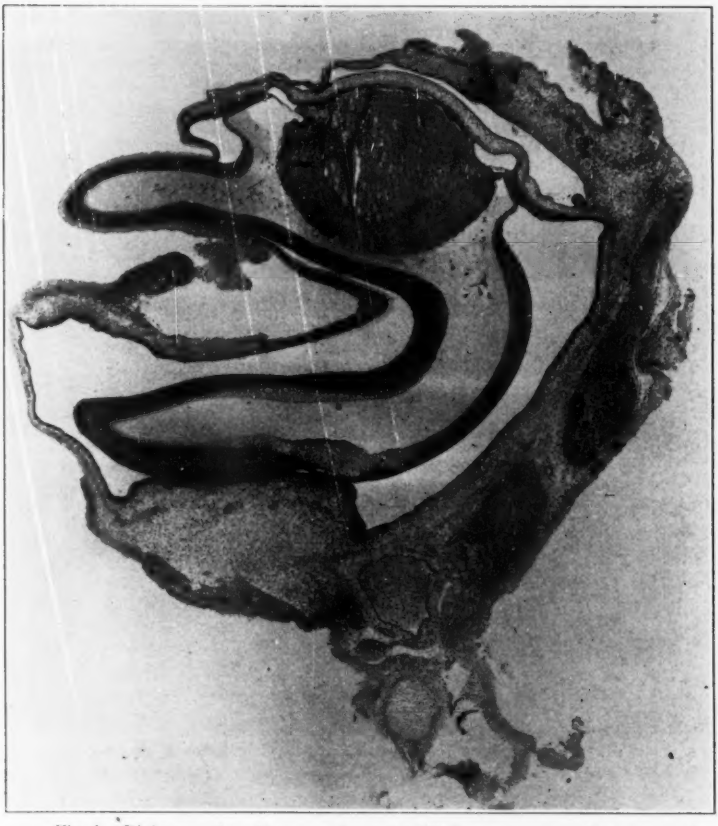

Fig. 1.—Right eye of an 11 mm. embryo (× 25) from a woman who contracted rubella during the second month of pregnancy, showing degeneration of primary lens fibers and early liquefactions of the secondary fibers.

Sclera.—The sclera was represented by a very loose mesodermal tissue on the outer surface of the choroid. Some of the extraocular muscles were seen to become confluent with this mesoderm.

Retina.—The retina was separated and somewhat folded, owing to shrinkage, but the nuclear and fiber layers appeared intact. The posterior portion of the

retina showed differentiation into two well defined nuclear layers, but anteriorly the differentiation was not so sharp.

Vitreous.—The primary vitreous occupied most of the cavity of the globe, and only a small amount of secondary vitreous was present. The vessels in the primary vitreous were filled with blood. Those of the tunica vasculosa lentis were also present and well developed.

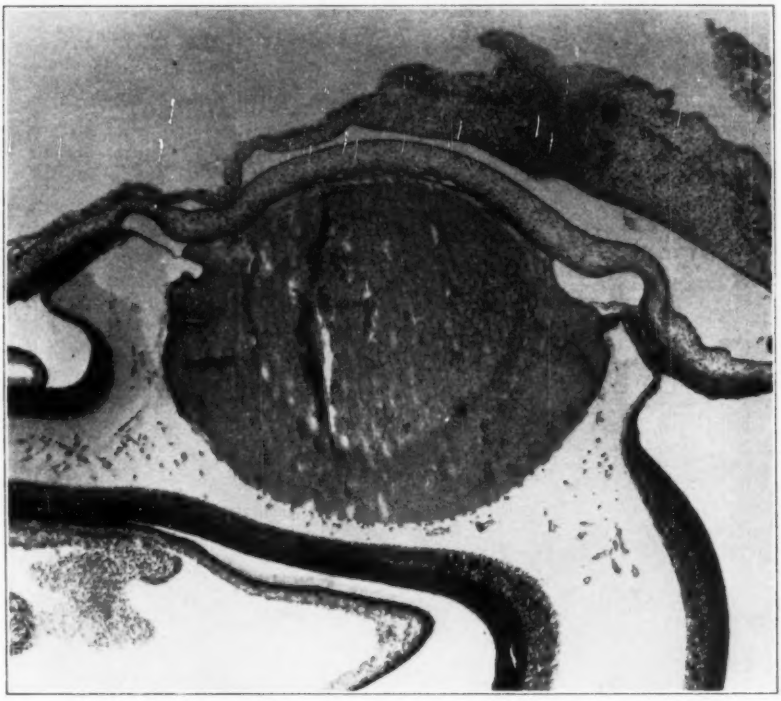

Fig. 2.—Higher magnification of the eye presented in figure 1, showing details of degenerative changes in the lens (× 42).

Lens.—The lens was rather large and rounded. The capsule was present and intact. Most of the primary and secondary lens fibers showed degeneration and liquefaction, with formation of globules and homogeneous masses of dark-staining fluid. The nuclei of the secondary lens fibers were of normal size and showed no degeneration. The nuclei of the primary lens fibers showed pyknosis and fragmentation (fig. 2).

Diagnosis.—The diagnosis was acquired cataract, due to rubella in the mother.

LEFT EYE

Gross Examination.—The eye measured 5 by 5 by 4 cm. The cornea was clear, and there was practically no anterior chamber, owing to the large size of the lens. The lens was milky white and opaque. The sclera was thin.

Microscopic Examination.—The cornea, anterior chamber, iris, ciliary body, choroid, sclera, retina and vitreous resembled those structures in the right eye (fig. 3).

Lens.—The lens capsule was thin but intact. The anterior epithelium of the lens appeared normal. Most of the primary and secondary lens fibers showed diffuse degeneration with formation of globules and uniform dark-straining masses of fluid. The nuclei of the secondary lens fibers were intact and appeared fairly normal, while those of the primary fibers were pyknotic and showed degeneration. The chief damage to the lens appeared to be in the primary fibers (fig. 4).

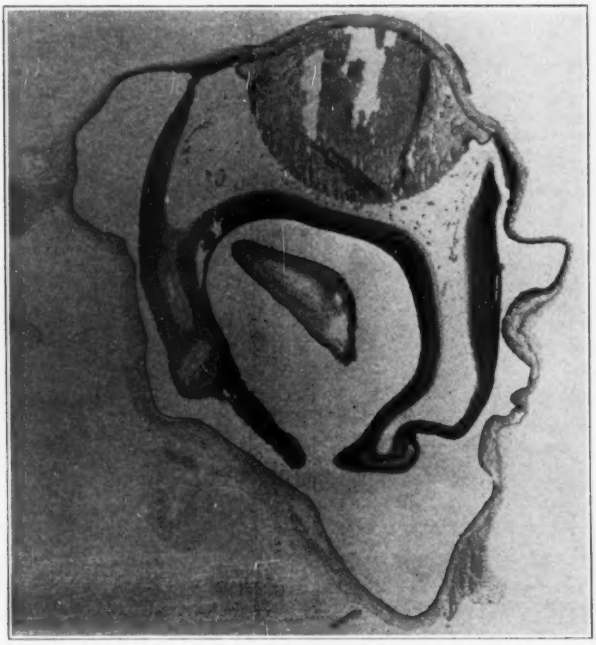

Fig. 3.—Left eye of the 11 mm. embryo whose eye is presented in figures 1 and 2, showing extensive degeneration of both primary and secondary lens fibers (× 25).

Diagnosis.—The diagnosis was acquired cataract, due to rubella.

Thus, the eyes of this 11 week embryo, with a history of rubella during the last part of the second month of gestation, showed cataract formation.

Three Additional Embryos.—During the early part of 1949, 3 additional embryos were received.

Specimen 2.—A 2½ month embryo was received with the history that the mother had had a therapeutic abortion three weeks after a severe illness of rubella. Serial section failed to reveal cataract formation or any other abnormality of the eyes.

Specimen 3.—A 3½ month fetus was received from another hospital with the history that two weeks before the pregnancy had been terminated the mother had a severe episode of rubella. Examination failed to show any evidence of cataract formation or other ocular anomaly.

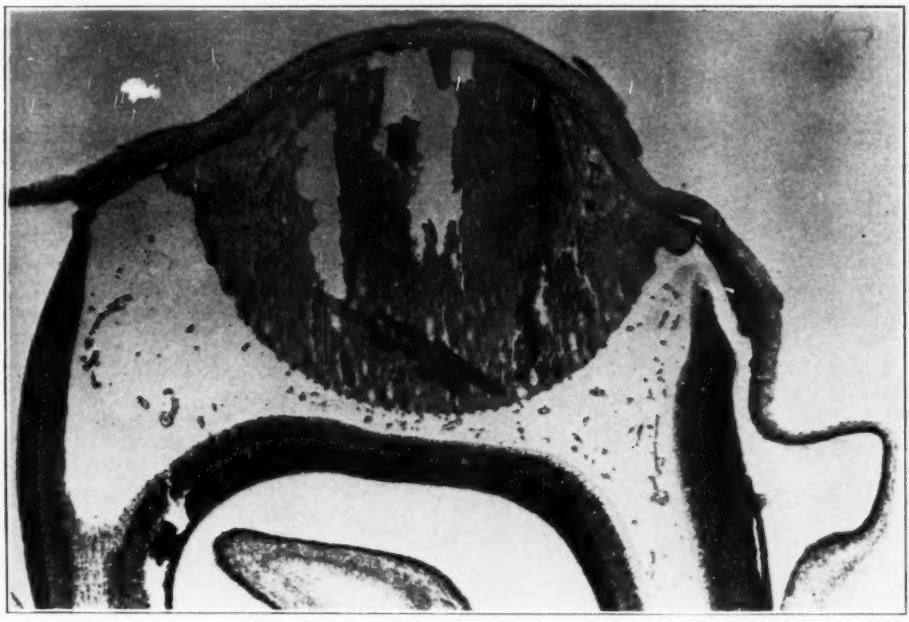

Fig. 4.—Higher power magnification of the eye shown in figure 3, showing details of degenerative changes in the lens (× 42).

Specimen 4.—A 3 month embryo was obtained after a therapeutic abortion a short time after a severe episode of rubella. The lenses showed no evidence of cataract formation, and the eyes seemed entirely normal.

COMMENT

Specimen 1 represents the second reported case in which an embryo from a mother who had had rubella during the first trimester showed cataract formation. It is the first in which both eyes were involved. This case, together with Swan's[5] and the case reported by Cordes

and Barber,[6] would bear out the contention that the damage to the lens may occur during the acute phase of rubella.

It has been observed clinically that the condition may not be bilateral. That unilaterality is determined early in the development of the embryo is exemplified in the case reported by Swan.[5] In his case, cataract developed in the right eye, and the left eye was normal so far as could be determined.

The consensus regarding the frequency of congenital defects following rubella during the first trimester of pregnancy has changed a great deal during the last five years. In 1944 Swan [5] stated that if a woman contracted rubella within the first two months of pregnancy the chances of her bearing a congenitally defective infant appeared to be in the region of 100 per cent. In 1947 Swan, Tostevin and Black [8] stated that it is possible that rubella in early pregnancy is not invariably followed by congenital defects in the offspring. In their combined series of cases, however, only 3 of the 62 babies whose mothers had had the infection during the first two months of pregnancy were free of congenital abnormalities. In an editorial appearing in the *British Medical Journal* [9] in 1946 it was stated that from the available evidence it appeared that the chance of rubella affecting the fetus if the disease was contracted by the mother during the first months of pregnancy was 10 per cent. In 1947 Aycock and Ingolls [10] found that, according to American statistics, defects occurred in only 25 per cent of the children whose mothers had rubella in the first three months of pregnancy. In 1947 Wesselhoeft [11] stated that a woman contracting rubella during pregnancy had approximately 1 chance in 10 of subsequently being delivered of a congenitally defective child. The preliminary report on the relation of various infections occurring in the first trimester of pregnancy to defects in offspring, sent out by Dr. Herbert C. Miller and his committee, has interesting figures on cataract formation. Of 89 children whose mothers had rubella during the first three months of pregnancy, 51 showed cataract formation. The highest incidence occurred in those cases in which the disease was present between the fifth and the eighth week.

8. Swan, C.; Tostevin, A. L., and Black, G. H.: Final Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy with Special Reference to Rubella, M. J. Australia **11**:889 (Dec.) 1946.

9. Rubella and Congenital Abnormalities, editorial, Brit. M. J. **2**:778 (Nov.) 1946.

10. Aycock, W. L., and Ingolls, T. H.: Maternal Disease As a Principle in the Epidemiology of Congenital Anomalies with a Review of Rubella, Am. J. M. Sc. **212**:366, 1946.

11. Wesselhoeft, C.: Rubella: German Measles (Concluded), New England J. Med. **236**:978 (July) 1947.

Thus it would appear that the incidence of cataract formation during the first three months is not as high as was originally believed. In this regard, it is interesting that there were no abnormalities of the lens in 2 of the specimens (2 and 4) for which there was a history of rubella during the first three months of pregnancy.

In discussing the low percentage of defects encountered in the American series, Swan, Tostevin and Black [6] suggested that there may be two strains of virus which produce rubella, one with, and one without, an affinity for embryonic tissues.

It is also of interest that in the preliminary report of Dr. Miller's committee, already mentioned, there was no evidence of cataract formation when rubella occurred after the third month of pregnancy. Thus, in specimen 3, the eye of an embryo from a woman who had rubella at the end of the third month, one would not expect to find cataract formation.

Bardram and Broendstrup,[12] in a review of this subject, stated that if fetal morbidity should prove to be fairly high, the question of therapeutic abortion must certainly be taken into consideration, especially since the effect of convalescent serum or similar therapy has not been ascertained. Swan and Tostevin [4] also stated the belief that, in the absence of effective prophylaxis, therapeutic abortion is entirely justifiable in the case of any woman who has rubella in the first four months of pregnancy. Other observers have voiced the same conviction.

This matter was discussed with Dr. Herbert Traut, professor of obstetrics and gynecology at the University of California. He stated that in the opinion of many leading obstetricians the termination of pregnancy in rubella is justifiable only under certain conditions: There must be a definite, unquestionable diagnosis of rubella in a severe epidemic. The infection must have occurred in the first trimester of pregnancy. From the ophthalmologic standpoint, clinical observations and the study of a limited number of embryos seem to corroborate these opinions.

Bardram and Broendstrup [12] suggested that all young girls be exposed to rubella as a prophylactic measure, since the mortality for all ages is reported to be only 1:50,000.

SUMMARY

The changes in the eyes of an 11 week old embryo are described. The mother had contracted rubella during the latter part of the second month of pregnancy. Both eyes of the embryo showed cataract formation.

12. Bardram, M., and Broendstrup, P.: Maternal Rubella Pregnancy As a Cause of Congenital Cataract and Other Congenital Malformations, Acta. ophth. **25**:352, 1947.

In addition, the findings in 3 other embryos are reported. The eyes showed no cataract formation.

A review of the literature and an examination of 5 specimens from mothers who had rubella during the first three months of pregnancy bear out the clinical findings that cataract formation is seen in a definite percentage of offspring in cases of maternal rubella. However, rubella contracted during the first trimester does not always result in changes in the lens.

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CYCLODIALYSIS

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AND
JACK WEIH, M.D.
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CYCLODIALYSIS as an operation for the relief of increased intraocular pressure has gained in favor with the staff of the ophthalmologic clinic at the University of Iowa until at present it is our operation of choice for chronic noncongestive wide angle or narrow angle glaucoma, hydrophthalmos and certain types of secondary glaucoma, notably that after cataract extraction. This paper is a report on the results of 100 consecutive operations made, with one exception, on patients with chronic primary glaucoma and followed for at least one year.

The literature on this operation has been covered thoroughly in the excellent reviews of Salus [1] in 1920 and Sugar [2] in 1947. Apparently, the first attempt to create an opening between the anterior chamber and the suprachoroidal space was reported by Querenghi [3] almost fifty years ago. However, Heine [4] (1905) devised the operation now known as cyclodialysis.

The purpose of each of the many operations for glaucoma is to lower and maintain within normal limits the damaging increased intraocular pressure. If one could only eliminate "maintain"! Cyclodialysis has been criticized severely by many surgeons because of its lack of permanent results. But what operation for glaucoma is invariably, or even usually, permanent? My personal opinion, substantiated by thirty years of experience, is that the tension after many so-called successful operations for glaucoma may, and often does, become elevated again after one, five or even ten or fifteen years. Only surgeons with little experi-

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1. Salus, R.: Die Zyklodialyse, Klin. Monatsschr. f. Augenh. **64**:433, 1920.

2. Sugar, H. S.: Cyclodialysis: A Follow-Up Study, Am. J. Ophth. **30**:843, 1947.

3. Querenghi, F.: Faits et raisons qui expliquent l'action de la sclero-iridéctomie et des autres operations succedanées (sclerotomie et incision de l'angle iridocornéen) dans le traitement du glaucome, Ann. d'ocul. **123**:441, 1900.

4. Heine, L.: Die Cyklodialyse, eine neue Glaukomoperation, Deutsches med. Wchnschr. **31**:284, 1905; Zur Therapie des Glaukoma, Ber. ü. d. Versamml. d. ophth. Gesellsch. **32**:3, 1906.

ence or those who do not follow carefully their results are optimistic about the surgical treatment of glaucoma.

Heine's original theory regarding cyclodialysis has been proved; i. e., the operation creates an opening between the anterior chamber and the suprauveal space; the aqueous is drained into this space and absorbed. Elschnig [5] (1932) demonstrated miscroscopically that a permanent cleft was established where the ciliary body had been separated by operation from the scleral spur. Vannas [6] in 1935 first reported gonioscopic evidence of a cleft in the angle of the anterior chamber after a successful cyclodialysis, a finding confirmed by Barkan and associates,[7] Sugar,[8] Burr [9] and others (fig. 1).

Heine's original technic of cyclodialysis has been modified by a number of surgeons, some of whom combined it with iridectomy, sclerectomy or iridencleisis. Others implanted foreign substances, such as horsehair, silk thread, eggshell membrane or magnesium, in an attempt to keep the

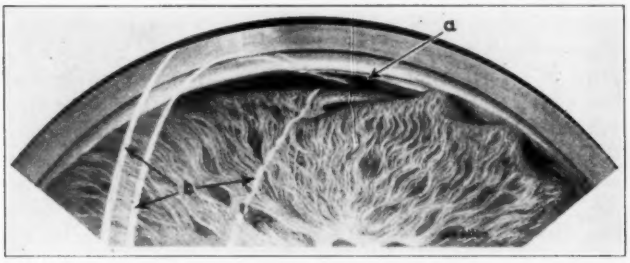

Fig. 1.—Angle of the anterior chamber as seen with the gonioscope and slit lamp: (*a*) cleft after a successful cyclodialysis; (*b*) optical section with the slit lamp beam.

cleft open. Blaskovics [10] modified the method of separating the ciliary body from the scleral spur and entitled it "inverse cyclodialysis"—the spatula was swept from the suprauveal space into the anterior chamber throughout the entire region of dialysis, and not from the anterior chamber toward the suprauveal space, as in the original operation.

5. Elschnig, A.: Zur Wirkungsweise der Cyclodialyse, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **49**:277, 1932.

6. Vannas, M.: Zykloskopische Untersuchungen über das Verhalten des Strahlenkörpers nach der Heinischen Operation, Klin. Monatsbl. f. Augenh. **95**: 629, 1935.

7. Barkan, O.; Boyle, S. F., and Maisler, S.: On the Surgery of Glaucoma: Mode of Action of Cyclodialysis, Am. J. Ophth. **19**:21, 1936.

8. Sugar, H. S.: Gonioscopy and Glaucoma, Arch. Ophth. **25**:674 (April) 1941.

9. Burr, S. P.: Personal communication to the authors.

10. Blaskovics, L.: Cyclodialysis inversa, Szemészet **70**:5, 1935.

CYCLODIALYSIS

Indications for Operation.—An operation for glaucoma is indicated when the intraocular pressure is elevated to such an extent that, in spite of drug therapy or any previous operation or operations, there is progressive loss of visual field. What is the average tension, as measured with the tonometer, above which one may expect trouble? It is our belief that a tension of over 22 mm. of mercury (Schiøtz) is usually pathologic. The field of vision should be checked carefully and repeatedly under identical conditions, i. e., the same size targets, at the same distance, with identical illumination and by the same technician.

It is suspected that in many cases in which the tension is found always to be within normal limits but the field is shrinking gradually there is at times an elevation of tension during the night.

Undoubtedly, early operation is best, i. e., before much loss of field occurs and before too many adhesions have formed in the chamber angle. But one must consider the age and life expectancy of the patient and the possible complications of operation, especially postoperative cataract. Indications for cyclodialysis vary with the surgeon; e. g., Ernst Fuchs resorted to it only after other operations had failed, while Barkan recommends it for both the wide angle and the narrow angle type of chronic noncongestive glaucoma and for certain types of secondary glaucoma. Although many surgeons apparently are not enthusiastic about this operation, it may be stated that some with great experience, namely, Elschnig, Blaskovics, Grosz and Gradle, employed the procedure often. Probably surgical results depend somewhat on the choice of cases and the technic of operation. Our personal feeling is that cyclodialysis is the operation of choice for any type of noncongestive glaucoma, for hydrophthalmos and for secondary glaucoma after cataract extraction, and as a second or third operation after any unsuccessful previous surgical attempt to lower the tension in cases of the aforementioned types of glaucoma. Furthermore, in many cases chronic congestive glaucoma responds to cyclodialysis. At the Iowa clinic the operation has grown gradually in favor until at present it is performed in more than 75 per cent of the cases of glaucoma in which surgical treatment is necessary.

Advantages of Cyclodialysis.—That the operation is comparatively harmless even in the hands of rather inexperienced surgeons is conceded. Certainly, it is less dangerous than any of the external filtering operations. Only in rare instances are harmful effects encountered, even though the cleft closes. The operation does not mar the appearance of the eye; it may be repeated once or several times, and secondary infection is exceedingly rare. The chances of success are lessened somewhat if the operation is repeated in the area of a former dialysis.

Disadvantages.—As occasionally occurs in any operation for glaucoma, the tension may not be lowered at all, or, if it is lowered, it may rise again sooner or later. Gát [11] stated that one disadvantage is the delay of three or four days between the operation and effective lowering of the intraocular pressure—we have not found it so with our present technic. Gát recommended posterior sclerotomy to lower the tension for the first few days, but it is believed that this procedure is not only unnecessary but inadvisable. Rarely profuse bleeding may occur at the time of operation or during convalescence. Cyclodialysis has been criticized for its lack of permanent results, but in our hands its effects have been as permanent as those of other operations.

Gonioscopic Studies.—It is imperative that the entire angle be examined carefully with the gonioscope and slit lamp in an effort to determine the proper site for operation. If possible, the dialysis is made in an area in which the angle is open and in which no large blood vessels are seen.

After operation a cleft in the chamber angle may be observed in almost every patient with a normal or low intraocular pressure. Occasionally the iris hump obscures the angle, but instillation of a miotic may allow study of this region.

Preoperative Routine.—Miosis is maintained up to the time of operation, and it is well to instil a strong miotic, such as 0.5 per cent solution of physostigmine salicylate, in each eye an hour or two before the patient is taken to the operating room. Typhoid H antigen, in a dose of 15,000,000 killed bacilli injected intravenously, is administered routinely on the day before operation. If the tension is high, 100 cc. of 50 per cent sorbitol may be injected into the vein the evening prior to operation, as advocated by Sanford Gifford. As a sedative, sodium bromide, grains 30 (2 Gm.), and chloral hydrate, grains 15 (1 Gm.), are administered in milk by mouth the night before operation and the administration is repeated the following morning one hour before the patient goes to operation. Pentobarbital sodium, grains 1½ (0.1 Gm.), may be added if necessary.

Local anesthesia is entirely satisfactory. A 0.5 per cent solution of tetracaine hydrochloride is instilled into the conjunctival sac every two minutes for five instillations and a retrobulbar injection of 2 cc. of 2 per cent procaine hydrochloride solution with epinephrine hydrochloride (1:20,000) is made into the muscle cone immediately behind the globe; this not only results in deep anesthesia but also lowers the intraocular pressure. Akinesia is of assistance and is used routinely.

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11. Gát, L.: Ueber die Wirksamkeit der modifizierten Cyklodialyse, Ophthalmologica **114**:106, 1947.

Technic of Cyclodialysis.—Several modifications of the original technic for cyclodialysis have been devised, the best known being Blaskovics' inverse cyclodialysis, described in 1935.

Barkan [12] advocated the use of a large conjunctival flap, a scleral incision 8 mm. back of the limbus and the injection of air for hemostasis and to make possible an immediate second dialysis in another quadrant.

The technic used at the Iowa clinic differs somewhat from both the original operation of Heine and Blaskovics' inverse cyclodialysis. As a rule, the superior temporal quadrant is chosen as the site of operation, since it is believed that the cleft is more liable to remain open permanently for the reason that if any hemorrhage occurs, the blood tends

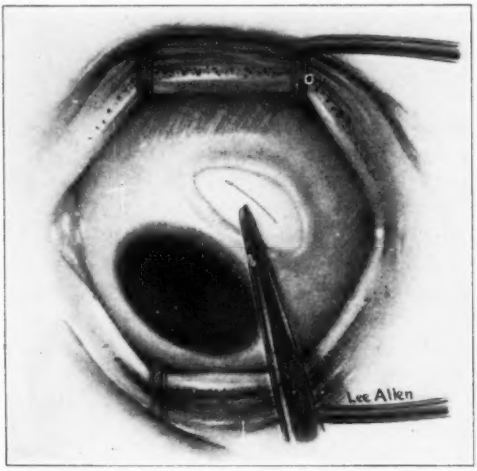

Fig. 2.—Scleral fixation with a 0000 silk suture grasped with a small hemostat.

to gravitate toward the lower portion of the anterior chamber and in this manner is carried away from the cleft. Furthermore, the dialyzed ciliary body has a tendency to sag downward and keep the cleft open if the patient is kept in a sitting position.

The conjunctival incision is approximately 8 mm. in length and is made parallel to and from 6 to 8 mm. back of the limbus, thus exposing an area of sclera in the upper (or lower) temporal quadrant. Next, the area for the intended scleral incision is selected between the insertions of the tendons of the lateral and superior rectus muscles.

12. Barkan, O.: Cyclodialysis, Multiple or Single, with Air Injection: An Operative Technique for Chronic Glaucoma, California Med. **67**:78, 1947.

Before the incision is made, a scleral fixation suture of 0000 silk is placed just anterior to the area of intended incision (fig. 2); the silk is grasped near the sclera with a mosquito hemostat, and the loose ends are cut away. Or one may tie two knots near the sclera, cut off the loose ends of silk and grasp the knots with forceps. Fixation by either method is quite secure. In order that undue bleeding in the area of the

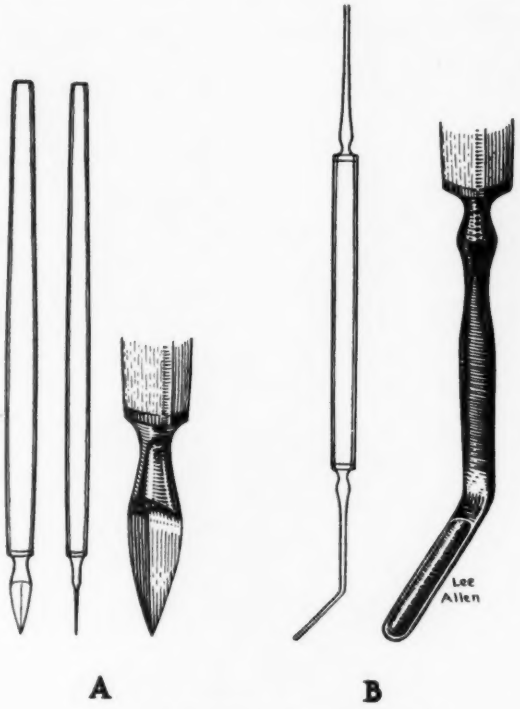

Fig. 3.—*A*, sclerotome; *B*, grooved spatula.

incision may be eliminated, a small muscle hook is heated slightly over an open flame and the sclera over the area of incision is touched very lightly with the heated instrument, thus coagulating the vessels. Next, the incision itself is made with either a sclerotome (fig. 3) or a Graefe knife; this incision is made approximately 4 mm. back of the limbus and is 3.5 to 4 mm. long, concentric with the limbus and slanted slightly forward as it passes through the sclera. Approximately one-half the

thickness of the sclera is incised with the first sweep of the knife; then, with the sharp point of the knife, the scleral tissue is picked carefully from within outward, great care being taken to cut all the fibers but

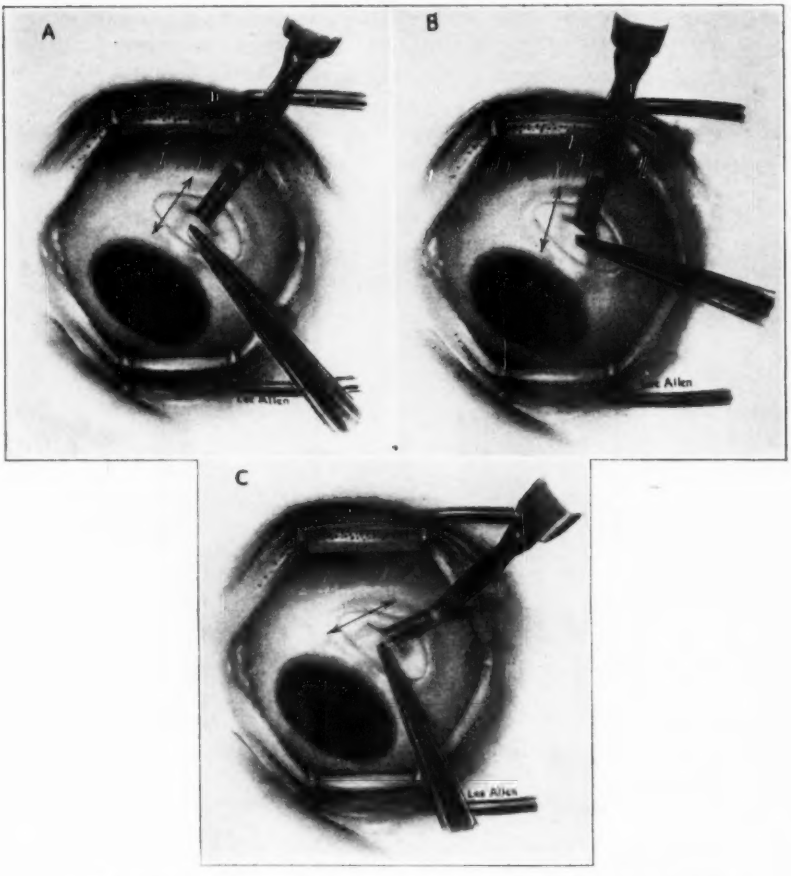

Fig. 4.—*A*, spatula passed inward and withdrawn in the direction of arrows; *B*, later stages of dialysis. Arrows indicate direction of the spatula. *C*, still later stages of dialysis.

to avoid injuring the underlying uvea. One must not pull on the fixation suture; otherwise the incision may tend to extend forward within the sclera rather than pass through, as intended.

A special grooved spatula (fig. 3), first recommended by Laird,[13] is used for the actual dialysis. The anterior lip of the scleral wound is lifted with the fixation suture, and the spatula is made to depress the posterior lip; then, with the tip pointing forward, the instrument is inserted slowly and carefully, its tip hugging the inside of the sclera at all times. The spatula is not at any time pointed toward the vitreous. As soon as the tip of the instrument is viewed in the periphery of the anterior chamber (fig. 4 *A*), the spatula is withdrawn slightly, and then, by repeated thrusts of the tip of the instrument through the region of the scleral spur (fig. 4 *B* and *C*), almost one-half the attachment of the

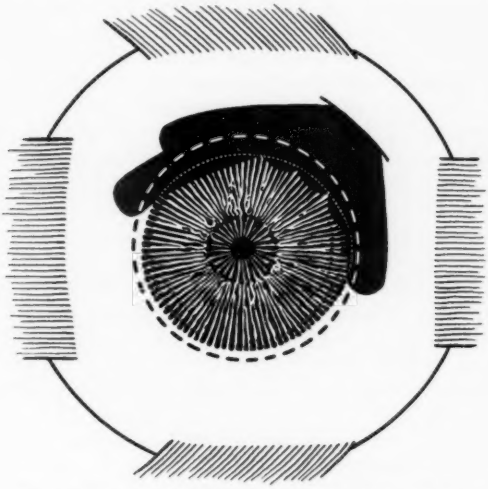

Fig. 5.—Extent of dialysis as shown by darkened area.

ciliary body is torn loose (fig. 5). The sweeping motion as advocated by Heine, or that made in the opposite direction, as described by Blaskovics, is not used. Great care is exerted not to enter far into the anterior chamber, since it is believed that the endothelium of the cornea, Descemet's membrane and the crystalline lens are then more liable to severe injury.

The groove in the spatula is utilized to draw the blood from the area of operation during the few minutes in which bleeding usually occurs. The blood is withdrawn by applying sharp-pointed, moistened, sterile cotton dental swabs to the portion of the groove situated just

13. Laird, R. G.: Personal communication to the authors.

outside the incision. In this way, little or no blood remains in the region of the cleft or the angle of the anterior chamber after the operation has been completed. It is believed that this technic is preferable to injection of air. It certainly keeps the cleft free from any hemorrhage which may organize at some later time and close the communication between the anterior chamber and the suprauveal space. Of course, it does not prevent the occasional delayed hemorrhage which may occur during convalescence.

As for actual dialysis, it is believed that the result is oftener permanent when almost one-half the attachment of the ciliary body is separated from the scleral spur. We feel that a smaller dialysis is much more likely to close and that this may be the reason that many surgeons object to this operation on the basis of lack of permanent results.

Injury to the anterior ciliary arteries may cause excessive hemorrhage. Consequently, during the process of dialysis the spatula is kept in front of these vessels. The anterior ciliary arteries perforate the sclera approximately 2 mm. anterior to the insertion of the tendons of each of the rectus muscles. The long posterior ciliary arteries are not injured, since they usually enter the posterior portion of the ciliary body and therefore are too far back unless the incision is made 7 to 8 mm. behind the limbus. With the technic here described, it is certainly unusual to injure these vessels.

In 1943 Randolph[14] first reported injection of air following cyclodialysis. Barkan expressed the belief that his technic of single or multiple cyclodialysis with injection of air produces less trauma and gives more permanent results than other methods.

The scleral wound may or may not be closed with a suture; a short incision, such as that used in our technic, usually does not require closure. The conjunctiva is closed with 0000 surgical gut or with 000000 silk sutures.

Postoperative Routine.—Immediately after operation 0.25 per cent solution of physostigmine salicylate is instilled in an effort to keep the dialyzed portion of the ciliary body away from its attachment. A dressing is applied over the closed lids and left in place for six to eight hours. The patient is asked to lie in bed twenty-four hours with the head elevated approximately 45 degrees and is requested to remain quiet as a guard against bleeding. Pilocarpine nitrate, 1 per cent solution, is instilled twice a day. If undue redness develops or evidence of early iritis appears, 5 per cent solution of cocaine hydrochloride and 1 per cent epinephrine bitartrate jelly are instilled once a day—this medication dilates the pupil temporarily and prevents formation of synechias. After this treatment the pupil is again contracted with pilocarpine. The patient

14. Randolph, M. E.: A New Cyclodialysis Instrument, Am. J. Ophth. **26**:187, 1943.

is allowed out of bed after the first day. Gentle massage, an important part of the postoperative treatment, is instituted on the day following operation and is continued twice daily for several weeks, being carried out by the physician while the patient remains in the hospital and after this time by the patient himself. During the first few postoperative days the massage must be gentle; otherwise it may cause hemorrhage.

Complications.—Complications may be encountered at the time of operation or during convalescence. Of the complicating factors which occur at operation, the one reported to be commonest is hemorrhage. With our present technic, this occurs rarely, perhaps because by preliminary gonioscopic examination we have learned the location of any large vessels in the angle of the anterior chamber and, furthermore, because we have exerted care to stay in front of the area in which the anterior ciliary arteries extended from the sclera into the ciliary body. With this technic of detaching the ciliary body from the scleral spur, it is unnecessary to sweep the spatula over the region of the anterior ciliary vessels. Furthermore, by removing the blood which flows outward along the grooved spatula and by continuing to do this until bleeding stops, it is unusual for an eye to contain much free blood when the patient leaves the operating room.

Delayed hemorrhage is another matter. Bed rest for twenty-four hours, with limited activity for a few days, is apparently the best preventive. Of the 100 cases reported here, there were 3 with severe postoperative hemorrhage occurring on the first or second day after operation. One of these eyes had an eventual rise in tension; a second became blind, but not painful, and the third had to be enucleated. The belief that large, and perhaps some moderate-sized, hemorrhages are prone to result in closure of the cleft is probably true.

Occasionally, especially with inexperienced surgeons, all the scleral fibers may not be severed at the time of incision, and undue pressure with the spatula may result in sudden plunging of this instrument through the choroid and into the vitreous. Such a complication may be prevented if all the scleral fibers are cut, if only gentle pressure is used to insert the spatula into the wound and if the anterior lip of the wound is lifted with the fixation suture and the direction of the spatula is forward and along the inside of the sclera, rather than toward the choroid and vitreous. This complication occurred in 2 of our cases; the tension was not controlled. Even though vitreous does present in the wound, the operation may be completed as usual.

If the spatula is not kept against the inside of the sclera, it may penetrate the root of the iris, and the tip will then pass into the posterior chamber. Injury to the lens may follow.

At times, when dense anterior peripheral synechias are present, the spatula meets with strong resistance. It is well to proceed carefully and to maintain control over the instrument at all times.

Lacerations of Descemet's membrane result from pressure with the spatula against the posterior surface of the cornea. Therefore, one must use great care to insert the spatula only a short distance into the anterior chamber, and it must be kept between and away from the posterior surface of the cornea and the root of the iris. If there is severe injury to the cornea, permanent opacity may result.

The commonest late complication, if it may be called a complication, is closure of the cleft with recurrence of the increased intraocular pressure. The operation is designated as a surgical failure if this occurs within a period of a few weeks or months. The tension was not controlled in 21 of the 100 cases under discussion. Occasionally the cleft may not close for several years, or the closure may follow other operative intervention, e. g., cataract extraction.

Changes in the refractive error are common after cyclodialysis; however, they often disappear gradually. Usually the refractive error is increased; i. e., hypermetropia is lessened or myopia increased.

Cataract is a common late complication. Of course, if the operation is made improperly and the lens is injured by the spatula, a cataract may develop with great rapidity. However, this complication is rare, but the slow development of cataract after a period of from one to ten years is common. It is our belief that after cyclodialysis, as well as after any of the external filtering operations, cataract not infrequently develops. After long experience, one of us (C. S. O'B.) has concluded that opacities in the lens develop gradually after operation for glaucoma in many more patients than the literature would lead one to believe. Therefore, in the decision to operate or not to operate for glaucoma, this factor must be considered, and I should go so far as to state that a patient should be warned of the possibilities of gradual loss of central vision and of eventual cataract extractions. Of the 79 cases of successful operation in this series of 100, there were some loss of central visual acuity in 23 eyes, loss of one line (Snellen chart) in 15 eyes, loss of two lines in 2 eyes and loss of more than two lines in 6 eyes. Our records did not state always the cause of visual loss, but often it was due to cataract.

Cataract extraction is more easily made after cyclodialysis than after external filtering operations, such as Elliot's trephine operation or the Lagrange procedure. One should suture the cataract wound securely in order that the anterior chamber will reform rapidly and in this manner lessen the chance of closure of the cyclodialysis cleft.

Another infrequent complication is low grade iridocyclitis, which may appear during the first or second week after operation. As a rule, this is a mild inflammation and may be controlled with a daily intravenous injection of typhoid H antigen. In order to prevent posterior synechias, one dilates the pupil temporarily, daily or every other day, with a 5 per cent solution of cocaine hydrochloride, followed with instillation

of 1 per cent epinephrine bitartrate jelly—this results in the pulling away of any newly formed adhesions. The administration of a 1 per cent solution of pilocarpine nitrate morning and evening is continued as usual. We were faced with this complication in 6 eyes, but in only 2 of them was the tension uncontrolled.

Hypotony is a rare complication of cyclodialysis—as a matter of fact, much rarer than after the external filtering operations. Even with large dialysis, such as is made in the Iowa clinic, tensions of 12 to 14 mm. extending over any prolonged period are extremely rare. It occurred in only 1 of the 100 cases.

In 1 eye there was some hemorrhage into the vitreous. Prolapse of a small knuckle of ciliary body has been seen, but this complication did not occur in this series of cases. Subluxation of the lens has been reported, but this we have not encountered, and it must be very unusual. Retinal detachment is also reported as a complication. A cystoid or ectatic scleral scar has been mentioned in the literature.

Results of Operation.—Cyclodialysis differs little from many other operations on the eye in that the results of the operation depend somewhat on the patient and the individual response of the eye to surgical intervention; they depend greatly on the surgeon's choice of operation, technical skill and surgical judgment.

Successful results from this operation have been reported in as few as 20 per cent of cases (Troncoso [15]) and in as many as 90 per cent (Barkan [12]).

What constitutes a successful result? The eye should be white and free from inflammation; the tension should remain within normal limits, and there should be no further loss of visual field. The last is the real criterion. Oftentimes there will be a slow but progressive loss of central vision as the result of changes in the lens, even though the aforementioned criteria for a successful result have been fulfilled. The question arises: Is this a successful result? Certainly, the patient has been freed from increased pressure and permanent loss of vision. Consequently, while it has not done all that may be desired, the operation must be considered successful, since if the tension is controlled it has accomplished its purpose. According to these criteria, the results in 79 of the 100 cases reported here were successful; i. e., the eye was not inflamed, the tension was 22 mm. of mercury or less (Schiøtz) and there was no loss of field for at least one year. In 24 of these 79 cases one or more previous operations had been performed for glaucoma.

The operation may be immediately successful but be followed within a few days, weeks or months by the return of increased intraocular

15. Troncoso, M. U.: Cyclodialysis with Insertion of a Metal Implant in the Treatment of Glaucoma, Arch. Ophth. **23**:270 (Feb.) 1940.

pressure, or it may be permanently successful. Perhaps the word "permanent" should not be used here, since a certain percentage of so-called permanent results eventually prove to be otherwise. We do not consider the operation effective unless the tension remains within normal limits (22 mm. of mercury or less, [Schiøtz]) with or without the use of miotics for at least one year. Certainly, one should never release from observation a patient who has once had glaucoma, no matter how successful the operation may seem.

In eyes in which the tension has been reduced, examination with the gonioscope almost always reveals an open cleft in the angle of the anterior chamber.

In most cases of successful operation the tension is from 14 to 18 mm. (Schiøtz) for a few weeks or months and then it gradually climbs to 20 to 22 mm. Some patients require massage or miotics, or even both, to control the pressure. Perhaps in patients who have an increased pressure which responds to miotics the iris plugs the cleft unless the pupil is contracted and the iris is pulled out of the angle.

Every ophthalmologist encounters patients in whom the postoperative intraocular pressure apparently remains within normal limits but the visual field continues to contract. Is this the type of patient whose eye cannot withstand an average normal intraocular pressure and whose tension must be less than the average to preserve function? Or is the condition a cavernous atrophy of the optic nerve? Or what is it? We believe that many patients of this type must have an elevated intraocular pressure at times, probably during the night; of course, this is not true of all such patients, and sometimes the loss of field remains inexplicable.

In behalf of cyclodialysis, it may be stated that the operation may be repeated one or more times with an excellent chance of success if the second operation is made in another area, but with some chance even if the operation is repeated in the area of previous dialysis. Some surgeons believe that second operations are almost always ineffective, but this is open to question; e. g., in 2 eyes the third cyclodialysis controlled the tension.

SUMMARY AND CONCLUSIONS

Cyclodialysis is the operation of choice for chronic noncongestive glaucoma (wide angle and narrow angle types); in an opinion based on data other than those discussed in this paper, it is the operation of choice for hydrophthalmos and for the secondary glaucoma which follows cataract extraction.

The operation is oftener successful if extensive dialysis is performed, i. e., separation of almost one-half the attachment to the scleral spur. Bleeding must be controlled if results are to be satisfactory.

The operations reported here were performed by various members of the staff (including the resident staff), and almost all were performed prior to 1946. It is believed that the results are better at present, since improvements in technic have been made.

The results of 100 consecutive operations on eyes with chronic primary glaucoma are summarized in the accompanying tabulation.

	No. of Cases
Cyclodialysis	100
Successful (for at least 1 year)	79
Unsuccessful	21
Reoperation (one or more times)	14
Cyclodialysis	5
Successful	1
Unsuccessful	4
Other operations	9
Complications	
Hemorrhage in anterior chamber	47
Severe	3
Moderate	7
Mild	37
Iridocyclitis	6
Severe	2
Mild	4
Loss of vitreous	2
Hemorrhage in vitreous	1
Hypotony	1
Diminution of visual acuity (usually cataract)	23

DETACHMENT OF THE RETINA IN EARLY SARCOMA (MALIGNANT MELANOMA) OF THE CHOROID

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NEW YORK

IN THE beginning of its growth sarcoma of the choroid does not cause detachment of the retina. It is after the tumor becomes larger that it causes the retina to separate from the choroid, and into the space thus formed an albuminous fluid is extravasated (serous detachment). Not infrequently the retina remains adherent to the head of the sarcoma —solid detachment—while along its sides the fluid presses the retina away from both the tumor and the choroid. The present paper is concerned only with the early stage of the detachment, before it has become total and before glaucoma has set in.

At a meeting of the Ophthalmological Society of Vienna in 1935, Salzmann [1] showed microscopic preparations of early sarcoma of the choroid in which, in addition to the ophthalmoscopically visible detachment of the retina confined to the neighborhood of the tumor, there existed on the opposite side of the fundus a circumscribed slitlike separation.

A short time afterward, A. Fuchs [2] reported 4 cases of a vesicular detachment of the retina immediately below the ora serrata. This detachment was far removed from the tumor and was apparently independent of the slitlike separation described by Salzmann, which was also present in all 4 cases. To the slitlike detachment, Fuchs gave the name *minimale Netzhautabhebung* (minimal retinal detachment) and to the one at the ora serrata, the name *Netzhautabhebung an der Ora serrata.* Thus, two new terms were added to the many in the nomenclature of retinal detachment.

In a second paper, Fuchs [3] reported 5 more cases of detachment at the ora serrata. As so often happens when one believes one has run

1. Salzmann, M.: Klin. Monatsbl. f. Augenh. 1935, vol. 95; Ueber Frühstadien des Sarkoms der Aderhaut und die histologischen Grundlagen des Augenspiegelbildes, Ztschr. f. Augenh. **88**:185 (Feb.) 1936.

2. Fuchs, A.: Ueber umschriebene Netzhautabhebung an der Ora serrata bei beginnendem Sarkom der Aderhaut, Klin. Monatsbl. f. Augenh. **95**:1 (July) 1935.

3. Fuchs, A.: Zur klinischen Bedeutung der umschriebenen Netzhautabhebung an der Ora serrata bei beginnendem Aderhautsarkom, Klin. Monatsbl. f. Augenh. **98**:606 (May) 1937.

across something new in ocular pathology, Fuchs found, on consulting the literature, that his father, E. Fuchs,[4] had long before called attention to detachment at the ora serrata in a report of 2 cases.

PRESENT MATERIAL

To the reported 11 cases of circumscribed detachments of the retina, both minimal and at the ora serrata, associated with early sarcoma of the choroid, I am able to add 19 which were selected from the collection of sarcomatous globes in the museum of the Eno Laboratory at the New York Eye and Ear Infirmary. The tumors were of various shapes and sizes and were located in the posterior or the lateral portion of the fundus.

Minimal Detachment.—In 12 of the 19 cases, minimal detachment occurred at a distance from the primary detachment that surrounded the tumor. The height of the separation ranged from 0.125 to 0.2 mm.; only once did it attain 0.5 to 1 mm. The area of the fundus involved varied a great deal. In 5 cases it covered the entire side opposite the tumor, reaching as far as the ora serrata. At times the greater part of the retina appeared to be more or less detached (figs. 1 *A*; 2 *A*; 3 *A*; 4 *A* and *B*). Occasionally the detached area was very limited, being confined to the other side of the papilla (fig. 1 *B*).

In a number of cases there were several separate minimal detachments (figs. 2 *B* and *C*; 3 *B* and *C*). Some of these spaces may have been cross sections of irregular borders of one extensive and continuous detachment. As a rule, when the slits were multiple, one was found on the opposite side of the papilla and the other in the corresponding equatorial region.

Oral Detachment.—In 10 of the 19 cases there was a circumscribed vesicular detachment immediately behind the ora serrata or 1 to 2 mm. from it (figs. 1 *B, C* and *D*; 2 *B, C* and *D*; 3 *B* and *C*; 4 *C* and *D*). The height varied from 0.1 to 0.2 mm., several times attaining 1 to 2 mm. The extent of the detachment ranged from 1 to 4 mm., the greatest being 6 mm. In 4 cases there was a detachment at the ora serrata without a minimal detachment (figs. 1 *D*, 2 *D*, 3 *D* and 4 *C*). Of the cases of combined detachment, a small detachment occurred at the papilla in 1, and two slits, one next to the papilla and the other at the equator, in another.

Proofs of Intravital Detachment.—The fluid in the spaces had taken a deep pink color from its albuminous content, as is usual in cases of

4. Fuchs, E.: Ueber Pigmentierung, Melanom and Sarkom der Aderhaut, Arch. f. Ophth. **94**:43, 1917; Klin. Monatsbl. f. Augenh. **98**:5, 1937.

sarcoma of the choroid, in contrast to the faintly stained Blessig's cysts at the ora serrata. Between the 2 fluid systems there was never any evidence of communication. Not infrequently cellular elements were seen in the subretinal fluid. The damage to the rods and

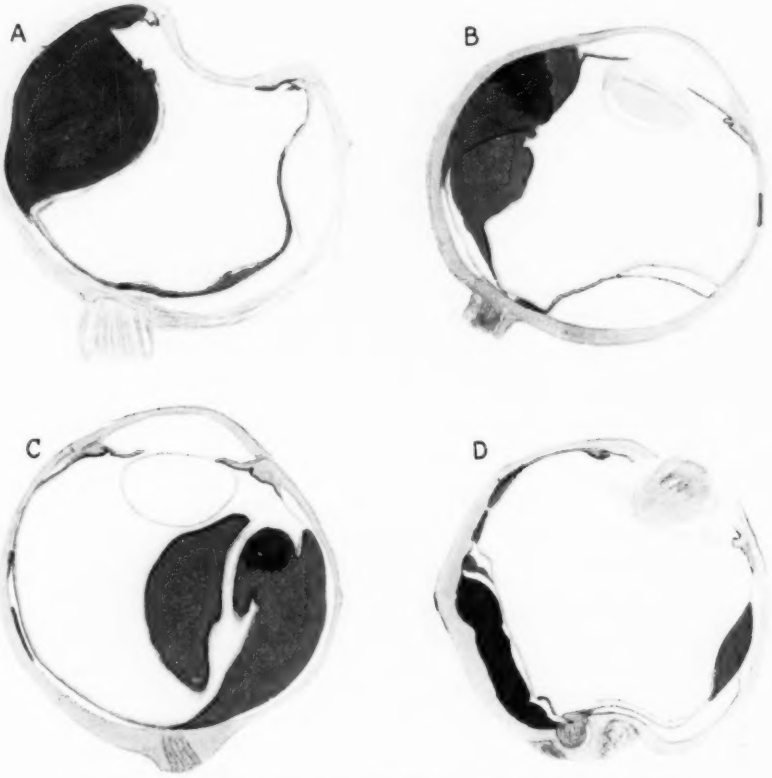

Fig. 1.—*A*, malignant melanosarcoma of the choroid and ciliary body. A minimal detachment embraces the entire opposite side. *B*, malignant melanoma of the choroid and ciliary body; circumpapillary minimal detachment opposite the tumor, with distant detachment at the ora serrata. *C*, melanosarcoma of the choroid, with two independent slitlike detachments opposite the tumor. *D*, vesicle-like detachment at the equator opposite the tumor. A long posterior artery is shown. A section of the cornea has been removed for keratoplasty.

cones was far greater than would probably have occurred, in the same period of time, in such small cavities in a case of spontaneous or

traumatic detachment. At many points the rods and cones were missing, and at others they had dissolved into drops, all of which indicated extraordinary toxicity on the part of the fluid.

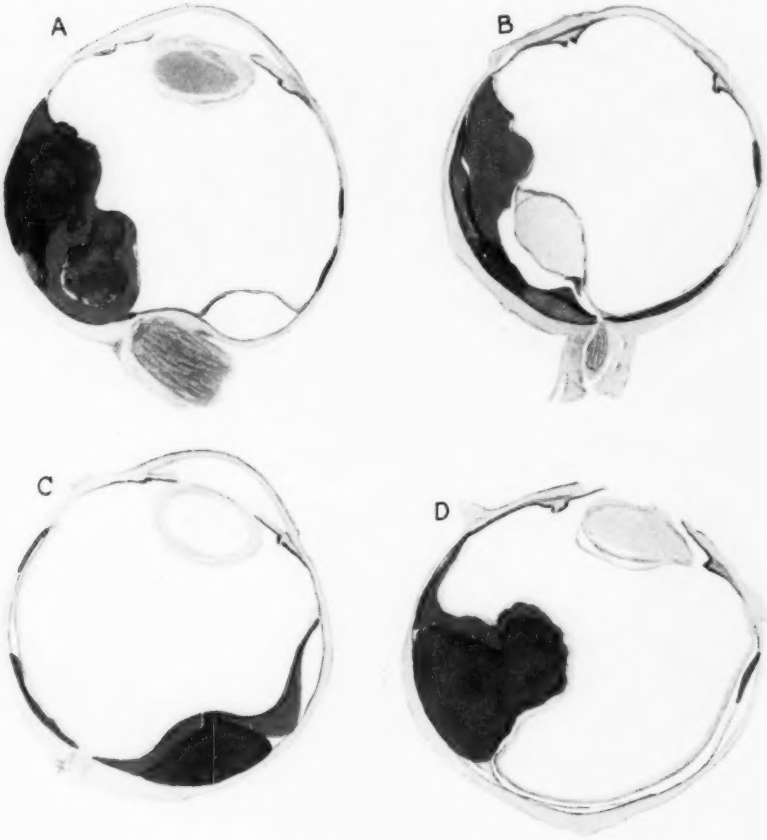

Fig. 2.—*A*, circumpapillary detachment; two separate minimal detachments opposite the malignant melanoma. *B*, independent, flat detachment at the ora serrata opposite the tumor, independent of the circumpapillary detachment. *C*, complete detachment on the side of the tumor and around the nerve head; independent, slitlike detachment at the ora serrata opposite the tumor. *D*, small slitlike detachment at the ora serrata opposite the tumor. A corneal section has been removed for keratoplasty.

RELATION OF MINIMAL RETINAL DETACHMENT AND DETACHMENTS AT THE ORA SERRATA

The slides available for study were cut in a meridional direction. In a given case of combined minimal detachment of the retina and

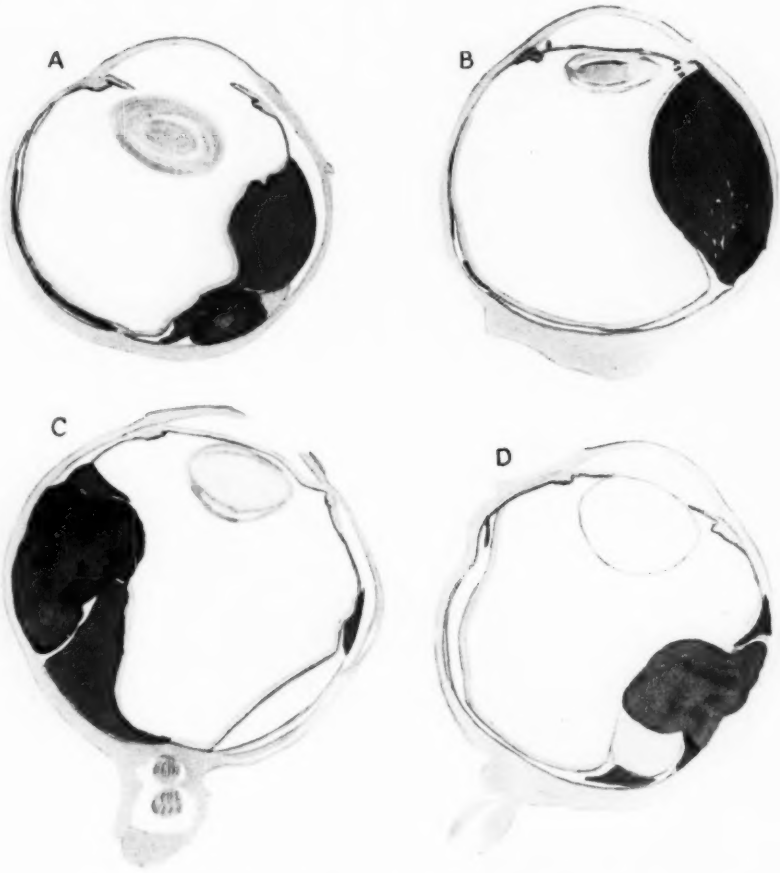

Fig. 3.—*A*, minimal detachment occupying the entire side opposite the tumor. *B*, three small minimal detachments opposite a large malignant melanoma. The retina has remained attached to the tumor. *C*, vesicle-like detachment at the ora serrata opposite the tumor. *D*, mere slitlike detachment opposite the mushroom-shaped malignant melanoma.

detachment at the ora serrata, frontal and serial sections might have proved the existence of a single continuous, thin sheet of serous fluid that had spread out from the primary fluid at the site of the tumor.

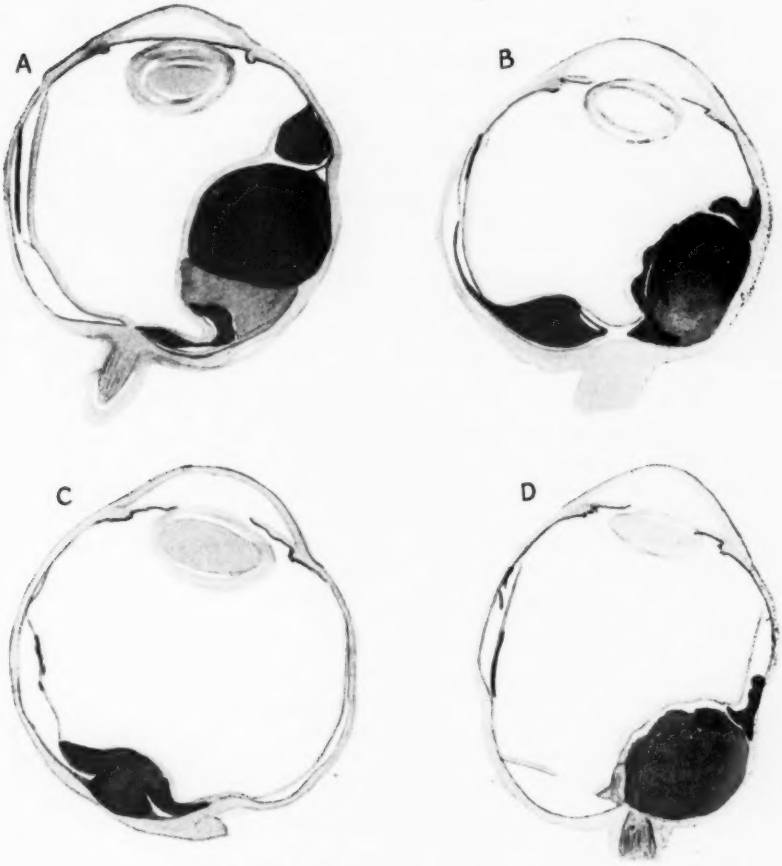

Fig. 4.—*A*, elongated, slitlike detachment opposite the ora serrata. *B*, slitlike detachment at the ora serrata, probably communicating with an extensive posterior detachment on the same side, opposite the tumor. *C*, slitlike detachment at the ora serrata, apparently independent, on the same side as the tumor. *D*, elongated, slitlike detachment at the ora serrata opposite the tumor.

No doubt the fluid was under a certain pressure. It is understandable that once it had reached a point at the ora serrata, where

most of the spontaneous and traumatic detachments occur, and where in infants' eyes the fold of Lange develops, the fluid gathered there and brought about the completed ring-shaped detachment at the ora serrata that was seen a number of times. There is little doubt that the disappearance of the rods and cones went hand in hand with the advance of the fluid and aided in the formation of the long narrow fissures between the pigment epithelium and the retina. There were cases in which the current in the fluid at the ora serrata appeared to have reversed itself and sent an extension posteriorly.

After all, from the anatomic standpoint, minimal retinal detachments and detachments at the ora serrata must represent steps in the progress of a sarcomatous separation of the retina the end of which is total detachment.

SOURCE OF THE FLUID

Since the subretinal fluid first attracts attention over a zone of immensely dilated and engorged blood vessels of the choroid at the base of the tumor, the most generally accepted theory is that the source of the fluid lies in this part of the choroid over which it first gathers. Here the choroid is many times the normal thickness. It is not unlikely that the tumor, the surface of which forms a part of the wall of the subretinal space, makes some contribution to the amount of fluid, particularly to the toxic element. At all events, the fact that the fluid, whether in a minimal retinal cavity or in a cavity in the ora serrata, took exactly the same stain as it did adjacent to the tumor speaks in favor of its being one continuous body. At distant points the choroidal vessels appeared not to be dilated, even under an area where the neuroepithelial layers of the retina were most damaged. Surely the highly albuminous fluid in a tumor-shaped cavity at the ora serrata could not have come locally from the choroid and retina, which are here poorly supplied with blood. As the detachment progresses to completion, it may be that vessels of the choroid remote from the tumor add their share of fluid, the greater part of which would probably continue to come from the site of the tumor, which by its replacement of the stroma mechanically interferes with the normal circulation.

CLINICAL SIGNIFICANCE OF MINIMAL RETINAL DETACHMENTS AND DETACHMENT AT THE ORA SERRATA

The clinical recognition of minimal retinal detachment is difficult, particularly since there are no folds in the retina, the underlying fluid being too shallow to permit them to form. Indeed, this type of detachment might be referred to as the clinically "invisible type." However, the transparency of the retina may be so impaired as to cause the markings of the choroid to be indistinct. A reduction in

the field for blue corresponding to an area distant from the tumor should arouse suspicion of a minimal detachment.

With respect to the clinical recognition of detachment at the ora serrata, the extreme periphery of the retina is normally blind and is inaccessible with the ophthalmoscope unless the method of making pressure on the wall of the globe with the finger, as described by Trantas,[5] is employed. It is possible, however, that with careful search one may discover such a detachment, one that extends far back, using the indirect method of ophthalmoscopic examination. Finally, minimal detachments of the retina and those at the ora serrata clinically and anatomically would seem to be so characteristic of early sarcoma of the choroid as to be of pathognomonic importance.

57 West Fifty-Seventh Street.

5. Trantas, A.: Moyen d'explorer par l'ophthalmoscope et par l'ophthalmoscope et par translucidité la parti antàrieure du fond oculaire, le cercle cilaire y compris, Arch. d'opht. 1900; Ophthalmoscopie du corps ciliare, Gaz. med. d'orient.

USE OF HYALURONIDASE WITH LOCAL ANESTHESIA IN OPHTHALMOLOGY

Preliminary Report

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THE ADVANTAGE of greater diffusion of an anesthetic solution for retrobulbar injection and nerve block is immediately apparent.

After Hoffman and Duran-Reynals [1] and McClean [2] reported the "spreading factor" of a substance found in the testes of normal rabbits, the use of this substance to increase the spread of anesthetic occurred to me. In 1936 I made a series of injections on rabbits to estimate the spread or diffusion of a solution of procaine hydrochloride with the addition of testicular extract. Ferric chloride was added to the solution to show the extent of diffusion when the tissues were sectioned and stained with Perles' stain. There was a marked increase in diffusion following injections in which testicular extract had been added to the anesthetic solution.

A subconjunctival injection of procaine hydrochloride with testicular extract was also given in one eye of a series of rabbits, and a control injection using procaine hydrochloride solution without testicular extract, in the other eye. The eyes were enucleated one, two and five minutes after the injection. The two eyes of a rabbit which had been enucleated five minutes after the injection were examined by Dr. A. B. Reese, who reported a much greater diffusion in the specimen in which the testicular extract had been added to the anesthetic solution. Although convinced that the testicular extract increased the diffusion of the anesthetic solution, the stimulation of cell growth in vitro by testicular extract, reported by Carrel,[3] and of Rous sarcoma (chicken tumor I), reported later by Hoffman, Parker and Walker,[4] suggested the possibility of undesirable side effects and discouraged its clinical use.

As the study of the mucopolysaccharides and mucolytic enzymes progressed, hyaluronidase was found to be the factor in testis responsible for the spreading. The enzyme hyaluronidase was first isolated

1. Hoffman, D. C., and Duran-Reynals, F.: J. Exper. Med. **53**:387, 1931.
2. McClean, D.: J. Path. & Bact. **34**:459, 1931.
3. Carrel, A.: J. Exper. & Med. **17**:14, 1913.
4. Hoffman, D. C.; Parker, F., Jr., and Walker, T. T.: Am. J. Path. **7**:523, 1931.

by Meyer and associates [5] from patients with type II pneumonia. Later a wide distribution was reported by Meyer and associates [6] and also by Chain and Duthie.[7] Besides being present in micro-organisms, its occurrence in the animal body in extracts of spleen, testis, ciliary body and iris has been demonstrated.

According to Meyer,[8] the action of hyaluronidase depolymerizes and hydrolyzes hyaluronic acid, a mucopolysaccharide acid, which was first isolated by Meyer and Palmer [9] from bovine vitreous humor. Subsequently, Meyer and his co-workers found it in the human umbilical cord,[10] bovine aqueous and vitreous of pigs,[11] bovine and human synovial fluid,[12] mesenchymal tumors [13] and the skin of pigs.[14] In animal tissue hyaluronic acid seems to bind water in interstitial spaces and holds cells together in a jelly-like matrix which obstructs diffusion.

Chain and Duthie [7] also observed that the hyaluronidase activity of testicular extract was similar to the "spreading factor" reported earlier by Hoffman and Duran-Reynals [1] and McClean.[2] These studies established the fact that the addition of hyaluronidase caused a rapid dispersion of fluid when injected into tissues. The rapid dispersion is brought about by a depolymerization and hydrolysis of the hyaluronic acid gel. The reduction in viscosity removes one of the barriers to diffusion of fluid and allows it to permeate the tissues more rapidly and widely.

The clinical use of hyaluronidase, until comparatively recently, has not seemed practical, as it was not readily available in purified form. Now a highly purified hyaluronidase [15] is available, and observations on its use with local anesthetic procedures about the eye are presented in this paper.

One hundred and nine preoperative injections of an anesthetic solution containing hyaluronidase were given. The surgical procedures included minor operations on the lids, cataract extractions, enucleations with implants and operations for glaucoma, retinal detachments and strabismus.

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5. Meyer, K.; Dubos, R., and Smyth, E. M.: Proc. Soc. Exper. Biol. & Med. **34**:816, 1936; J. Biol. Chem. **118**:71, 1937.

6. Meyer, K.; Hobby, G. L.; Chaffee, E., and Dawson, M. H.: J. Exper. Med. **71**:137, 1940.

7. Chain, E., and Duthie, E. S.: Nature, London **144**:977, 1939.

8. Meyer, K.: Physiol. Rev. **27**:3 and 335, 1947.

9. Meyer, K., and Palmer, J. W.: J. Biol. Chem. **107**:629, 1934.

10. Meyer, K., and Palmer, J. W.: J. Biol. Chem. **114**:689, 1936.

11. Meyer, K., and Palmer, J. W.: Am. J. Ophth. **19**:859, 1936.

12. Meyer, K.; Smyth, E. M., and Dawson, M. H.: J. Biol. Chem. **128**:319, 1939.

13. Meyer, K., and Chaffee, E.: J. Biol. Chem. **133**:83, 1940.

14. Meyer, K., and Chaffee, E.: J. Biol. Chem. **138**:491, 1941.

15. Hydase® (lyophilized hyaluronidase) for this study was supplied by Wyeth Incorporated, Philadelphia.

The anesthetic solution used was procaine hydrochloride, 2 per cent, with potassium sulfate, 0.4 per cent. One drop of epinephrine hydrochloride (1:1,000) and 30 turbidity-reducing units of hyaluronidase (hydase®) were added to each 5 cc. of the anesthetic solution. Two more drops of epinephrine hydrochloride were added for cone injections if not contraindicated.

In order to have a more concentrated solution of epinephrine for injections into the muscle cone and to avoid using more than 3 drops of epinephrine hydrochloride the following procedure was used: In a 5 cc. syringe containing 6 cc. of anesthetic solution, 1 drop of epinephrine was added. The injection of the temporofacial nerve at the site recommended by O'Brien [16] was first given, using about 3 cc.; 2 more drops of epinephrine hydrochloride were then added to the remainder in the syringe before giving the cone injection.

Without the use of hyaluronidase, excellent superficial anesthesia for surgical procedures on the lid and for minor operations on the globe is produced by subcutaneous and subconjunctival injections of a procaine-epinephrine solution. However, with hyaluronidase added to the anesthetic solution, there is less ballooning of the tissues, owing to rapid diffusion, and not as much procaine solution is required to produce the anesthesia. Massage following the injections further increases diffusion.

Although it has been possible to produce akinesia of the orbicularis muscle since 1914 by the method of blocking the branches of the temporofacial nerves, as advocated by van Lint,[17] and, later, by the more proximal injection suggested by O'Brien,[16] some surgeons experience difficulty in obtaining complete paralysis of the orbicularis. The addition of hyaluronidase practically obviates this difficulty, so that a second injection is rarely necessary.

To prevent loss of vitreous and other serious complications, temporary paralysis of the extraocular muscles is probably second in importance to the paralysis of the orbicularis muscles. While this can be produced by orbital injections of a procaine-epinephrine solution, often there is still some activity of the superior rectus and other muscles. The action of these muscles can be partially controlled by means of bridal sutures, but temporary paralysis of all the extraocular muscles would be preferable. Hyaluronidase added to the anesthetic solution used in a retrobulbar or cone injection followed by massage, as previously described,[18] accomplishes this in a higher percentage of cases. Injections

16. O'Brien, C. S.: Tr. Sect. Ophth., A. M. A., 1927, p. 250.

17. van Lint, M.: Ann. d'ocul. **151**:420, 1914.

18. Atkinson, W. S.: Local Anesthesia in Ophthalmology, Arch. Ophth. **30**: 777 (Dec.) 1943; Am. J. Ophth. **31**:1607, 1948.

into the muscle cone of more than 1.5 cc. may be safely given for cataract extraction because the solution diffuses rapidly. A more complete anesthesia of the orbital contents and paralysis of the muscles are thus obtained, and any proptosis subsides quickly. For enucleation, 5 cc. or more may be injected.

Hypotony has been more pronounced after cone injections with hyaluronidase added to the anesthetic solution. In 20 eyes with a normal intraocular pressure averaging 19 mm. Schiøtz, the decrease in pressure ranged from 6 to 9 mm. of mercury five minutes after the injection was given. In 2 cases, the pressure was unchanged at the end of five minutes, but at the end of ten minutes it had dropped 7 mm. of mercury in one eye and 8 mm. in the other eye.

The hypotony appeared even more pronounced after the section, and after extraction of the cataractous lens the cornea occasionally collapsed. On raising the corneal flap, one could see the surface of the vitreous well back of the plane of the iris. With such extreme hypotony the usual method of applying the hook is not as effective. Consequently, the mechanics of the intracapsular extraction, as described by Harrington,[19] are changed. The extraction is slower and more difficult. However, with the eye soft, it seems fair to assume that vitreous is less likely to prolapse. Possibly a change in the method of applying pressure and in the ratio of pressure to traction will facilitate the extraction in the presence of marked hypotony.

Whether the extreme hypotony is due to a greater relaxation of the extraocular muscles, to a more extensive constriction of the arteries entering the globe or to the depolymerization and hydrolysis of the hyaluronic acid in the vitreous, causing water to be released, is difficult to determine. Possibly it is a combination of all three factors. In any case, the problem is an interesting one and deserves study. It seems of particular importance because in eyes with glaucoma there is a more striking drop in the intraocular pressure than occurs after a cone injection without hyaluronidase. In a case of absolute glaucoma, the pressure, which was over 90 mm. Schiøtz before the injection, had dropped to 55 mm. Schiøtz five minutes after the injection.

In order that I might have data on a larger group of cases to study, Dr. John H. Dunnington has followed the same procedure on a series of cases. He feels that it is too soon for him to form a definite opinion in regard to the value of hyaluronidase in anesthesia. However, in a recent letter, he stated that the substance seemed to be of great help in producing akinesia and hypotony for cataract extractions.

My impression is that anesthesia is produced more rapidly when hyaluronidase is added to the anesthetic solution and that the duration

19. Harrington, D. O.: Tr. Am. Ophth. Soc. **46**:294, 1948.

of anesthesia is about the same as without it. Epinephrine was used in the anesthetic solution for all the injections. Kirby and associates [20] reported the duration of anesthesia to be about the same when epinephrine hydrochloride was added to the anesthetic solution of procaine hydrochloride with hyaluronidase but that it is shorter without the epinephrine. Another interesting observation of theirs was that "the degree of spread was greater when epinephrine was added to the procaine-hyaluronidase solution." This was attributed to the slower absorption due to the epinephrine.

For corneoscleral trephining in cases of glaucoma, a cone injection of procaine hydrochloride and epinephrine may lower the intraocular pressure to such a degree that the iris does not prolapse. The addition of hyaluronidase lowers it still further; so, unless a lower pressure is desired, a cone injection with or without hyaluronidase is contraindicated.

After an intradermal injection to produce a wheal, the site was at first ischemic, but the area of ischemia quickly disappeared and was followed by a corresponding area of erythema. Several minutes after a cone injection in which hyaluronidase had been added to the anesthetic solution, the conjunctival and episcleral vessels frequently filled with blood so that the eye was red even though it had previously been blanched with phenylephrine (neo-synephrine®), which had been used to dilate the pupil. No effect on the pupil attributable to the hyaluronidase was observed. The action of tetracaine (pontocaine®) hydrochloride as used for instillation anesthesia did not appear to be influenced by the addition of hyaluronidase.

SUMMARY

With the addition of hyaluronidase to injections of an anesthetic solution of procaine and epinephrine, the following observations were made:

1. There was a greater diffusion of the anesthetic solution.

2. Anesthesia occurred more rapidly than that induced by a solution without hyaluronidase, and the duration was about the same.

3. There was less ballooning of the tissues, and the area of anesthesia was greater.

4. More effective akinesia of the orbicularis and extraocular muscles was obtained.

5. Hypotony was pronounced after cone injections and was occasionally sufficient to make the cataract extraction more difficult but safer, with vitreous less likely to present.

20. Kirby, C. K.; Eckhenhoff, J. E., and Looby, J. P.: Surgery **25**:1 and 101, 1949.

6. Ischemia due to epinephrine was quickly followed by erythema, which was also of brief duration.

7. The eye frequently became red after a cone injection.

CONCLUSION

The addition of hyaluronidase to procaine-epinephrine solution enhances anesthesia and merits further study.

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SHORTENING OF THE EYEBALL FOR DETACHED RETINA

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IN 1931 I began to operate for retinal detachments which seemed otherwise incurable by shortening the eyeball. The technic of this operation was published in 1933.[1] In the United States, Pischel described this operation in the ARCHIVES in 1939.[2]

In this paper I wish to describe those details of the operation which I have changed since my first publication, enumerate the present indications for this operation and, finally, present the results. A detailed description of the operation appeared in "Ophthalmologische Operationslehre," edited by Thiel.[3]

If one shortens an eyeball, one diminishes its volume, and therefore an adequate amount of fluid must be drained from the eyeball during the operation. Prior to the time of the first publication, I tried to drain the eye by puncturing the exposed choroid with a discission needle (case 1). I did this using the Zeiss binocular magnifying lens and carefully avoiding any injury to the blood vessels. This type of drainage works well in cases of detachment in which the vitreous is so far detached posteriorly that the puncture hits the subvitreal space. This condition is met sometimes in aphakic eyes, especially in young persons. On the other hand, soon after performing this operation, my colleagues and I encountered cases in which the puncture of the exposed choroid released a little subretinal fluid and then the outflow stopped, because the retina became reattached. Then puncture of the attached retina led again to drainage, or the opening became closed by solid vitreous. In the latter case we perforated by coagulation more posteriorly, or we punctured the anterior chamber and opened the puncture opening repeatedly so that we could continue the shortening operation. In 1 of these cases the solid vitreous produced dilation of the needle opening in the choroid and retina and a solid prolapse appeared. I cut the prolapsing vitreous away, and a new mass of solid prolapse appeared, which I cut away again and again in order to lessen the volume of the eyeball and

1. Lindner, K.: Heilungsversuche bei prognostisch ungünstigen Fällen von Netzhautabhebung, Ztschr. f. Augenh. **81**:277, 1934.

2. Pischel, D. K., and Miller, M.: Retinal Detachment Cured by Eye-Ball Shortening Operations: Report of a Case, Arch. Ophth. **22**:974 (Dec.) 1939.

3. Thiel, R.: Ophthalmologische Operationslehre, Leipzig, Georg Thieme, 1943, vol. 2.

complete the shortening operation. But the retina of the other side was pulled toward the choroidal opening by the adherent solid vitreous, and the eye was lost.

Since this unfavorable result we have given up the puncturing of the exposed choroid, and we drain the eye only by perforating coagulations placed posterior to the detached vitreous. In shortening of the superior half of the eyeball, the perforating coagulations not only should drain the eye but should help to reattach a detached retina or to fasten an attached retina in place. When this drainage was arrested by the reattachment of the retina, we made a puncture again in the same place. If this did not help we made punctures more posteriorly or opened the anterior chamber and reopened the wound as often as necessary.

Hence, our present procedure is as follows: First, we must know the condition of the vitreous. The best way to examine the vitreous is with the slit lamp of Goldmann, in which the observation system and focused slit are moved together and are fitted, in addition, with the lens of Hruby and with his fixation lamp.[4] We must know how far the vitreous is detached posteriorly. For instance, if there is a flat posterior detachment, the strip to be excised should not be wider than 2 mm., for in cases of this type the eye is drained chiefly by puncturing the anterior chamber. From the anterior chamber we cannot remove sufficient fluid to allow the excision of a strip 3 mm. or more in width. However, in cases with the vitreous detachment far in front strips up to 6 mm. or more in width can be excised (case 5). Traction on the strands in the vitreous must be noted carefully, since they influence the method of operating (case 3).

We perform all shortening operations with local anesthesia. Our patients are tried for sensitivity to cocaine by injecting 1 cc. of a 1 per cent solution of cocaine subcutaneously. At the operation we inject a mixture of equal parts of 3 per cent cocaine and 2 per cent procaine hydrochloride. We add the 1:10,000 solution of ephinephrine hydrochloride in sufficient quantity to make it equal to one tenth of the total volume of the mixture. We use from 0.5 to 2 cc of this mixture. Sometimes in the case of elderly patients I have made several radial conjunctival incisions instead of a single circular one, to keep the cornea under better nutritional condition, although we never had complications due to insufficiency in this respect. The technic of incision of the sclera and of insertion of the sutures is the same as that which was described originally. Since 1945 we have used silk sutures and operate with cotton gloves. We had no sterile surgical gut. I emphasize the importance

4. Hruby, K.: Ueber eine wesentliche Vereinfachung der Untersuchung des hinteren Augenabschnittes im Lichtbüschel der Spaltlampe, Arch. f. Ophth. **143**:224, 1941; ibid. Klin. Monatsbl. f. Augenh. **108**:195, 1942.

of very sharp needles for suturing the sclera. I have found only those of Grieshaber (Schaffhausen, Switzerland) satisfactory. Not only is it difficult to operate with dull needles, but it is dangerous to the eye. Especially in areas which had been coagulated before the softened sclera may rupture from rough handling when dull needles are used. The sutures should be inserted outside coagulated areas in the sclera, because the latter do not give enough support to the sutures. In some cases I have excised the whole coagulated area. Therefore in all cases of detachment we observe the rule of coagulating as near the circumference of the holes as possible, if we choose this operative procedure.

The incision through the sclera at the beginning of the operation should be made before the eye is drained because of the difficulty of a through and through incision in the sclera in a soft eye.

I coagulate first with a blunt electrode and then use a perforating one inside the coagulated area to avoid hemorrhage. In some cases I insert Safar's double pins into the previously coagulated areas. The perforating needles must be 1.8 or 2 mm. long, for coagulated sclera is thicker than normal sclera. Then I begin the excision of the scleral strip at the place where the incision had already been carried down to the choroid. I expose no more choroid than an area which corresponds to one suture interval, so as to avoid the danger of rupture of the exposed choroid.

If the drainage stops, the retina most probably has become reattached in the perforated area. Then the retina must be perforated at the site of the electrocoagulation. If this is not followed by drainage, the perforation is made farther posteriorly, or the anterior chamber is punctured; for this purpose, the keratome of Wessely is used; an incision is made under a conjunctival flap, and the incision is reopened from time to time with a spatula. It may be necessary to wait several minutes before the anterior chamber refills with fluid and another puncture is made.

The greatest danger in this operation is that of an intraocular hemorrhage. It should be prevented by all means. Vortex veins must be avoided; if necessary, the scleral part where a vortex vein may be encountered is avoided (cases 1 and 2: shortening). If, with the strip, the scar of a former shortening (case 3, operation 4; case 4, shortening 2; case 5, shortening 2 and 3) is excised, the choroid is often found to be adherent to the area of the scar and must be carefully separated with a blunt spatula, just as when coagulated areas are excised. When an intraocular hemorrhage develops at operation, the eye is lost.

In several cases I tried to shorten the eyeball by folding a surgically thinned sclera instead of excising it in its whole thickness. However, after some initially good results, the condition in these cases became

worse. Therefore I have given up this method, since the folded sclera unfolded again when the stitches were absorbed (case 3). The technic to be described would have been less dangerous and much easier to perform than the excision. In some cases severe edema of the conjunctiva from lymphatic stasis developed a few days after the operation. Daily massage of the conjunctiva with a glass rod is necessary. In doing this we had no complications in the cornea. After this operation patients are kept in bed only four to five days.

We consider the following types of retinal detachment suitable for this operation:

1. Aphakic eyes without detectable holes. In such cases the vitreous is detached far forward (case 1).

2. Aphakic eyes in which operation had been performed for retinal holes without success (case 2).

3. Detachment with the retina fixed by strands in such a way that for mechanical reasons a reattachment was not possible (case 3).

4. Detachment operated on several times by the usual methods for which there is no hope of improving the condition by further surgical treatment of the same kind (cases 4 and 5).

What part of the eye should be shortened, and how often can an eye be shortened?

One can shorten an eyeball all around in one session.[1] I performed such an operation once without complications. However, the local anesthesia did not last long enough for me to complete the operation without pain in spite of repeated injections during the operation. Only general anesthesia, as used in the United States, would permit this long-lasting operation, in which I had to make radiating conjunctival incisions and a temporary resection of the internal rectus muscle. Therefore, I shorten only half the eyeball in one operation. The operation on the second half may be undertaken after an interval of three weeks.

If there was no binocular vision prior to the detachment, I shorten the upper half first. The operation on the lower half may follow, if necessary. Our aim is to reattach the upper half of the retina or to secure the reattachment of this portion of the retina because of the greater importance of the lower visual field. Perforating coagulations through the attached retina will keep this part of the retina in place later. In monocular cases the superior rectus is not reattached. On the contrary, I place a suture in the superior rectus, divide it, pull it away out and excise a piece of muscle. The remaining muscle slips back into the orbit. The same procedure is followed if the lower part of the eye is being shortened. In this way we lessen the dangerous vertical move-

ments of the eye. A remaining detachment in the lower part would not be influenced by lateral movements of the eye. The two oblique muscles are left uncut so as to preserve vertical mobility (Bell's movement to protect the cornea).

In eyes with vitreous strands preventing a reattachment, the scleral excision should be correctly placed to avoid the deleterious effect of traction by the strands. When coagulated areas are present, the surgeon may be forced to excise them or to operate in a different area.

In cases in which there was previous binocular vision and the other eye is intact, we prefer the shortening of the nasal side at the first operation. This has no influence on the vertical position of the eye. Slight horizontal deviations do not play such a disturbing role as do vertical deviations. After each shortening the eyeball becomes less mobile; it is preferable, therefore, to start with the more difficult (nasal) side. The operation on the temporal side may follow. If in such a case, for some special reason, the shortening of the upper or the lower half of the eye is desirable, I reattach the muscle as far back of its insertion as the strip is wide. But the muscle must always be reattached on the corneal side of the excised area; otherwise the wound would be opened. This detail should be considered in determining the placing of the excision.

Shortening operations were repeated several times in many cases in order to secure partial or total reattachment of the retina. The shortening operation may be considered as a race between the shrinking vitreous and the decrease in the size of the eye, which may continue for years (cases 1, 2 and 5). This race is lost if an intraocular hemorrhage takes place during the operation.

Twice I tried to excise radial strips of sclera with the idea of lengthening a hypermetropic eye rather than of shortening it. Besides, this technic may relieve the pull of the equatorially stretched vitreous. This technic did not work, as the choroid may fold on account of traction of the vortex veins. In circular excisions the choroid adapts itself easily to the shortened sclera.

To give an idea of the painstaking work connected with this difficult operation and the length of time it takes to obtain a satisfactory result, I submit several cases illustrating the various problems.

REPORT OF CASES

CASE 1.—Peter D., aged 29, had an operation for perinuclear cataract in 1938. This was soon followed by retinal detachment. Bed rest was prescribed and a compressing bandage was worn for a longer period. In April 1940 vision was very poor. The first examination, on Oct. 16, 1940, revealed that the left eye was blind, due to glaucoma and that in the right eye there was secondary cataract with

a very small hole in the secondary membrane. The retina showed a bullous detachment below and a flat detachment above; no hole was visible. Vision was limited to counting fingers, eccentric.

October 23, First Shortening (fig. 1 *A*): A strip 2 mm. wide from the upper half of the globe was excised. A suture was passed through the superior rectus, the muscle was pulled forward and a long piece of muscle was resected. The muscle was then allowed to slip back into the orbit. The exposed choroid was punctured in two places. The first puncture hole drained well. The second perforation showed a small pearl of solid vitreous. Therefore perforating coagulations were made temporally above. Owing to pressure, the vitreous pearl burst and some fluid escaped.

December 19: Vision with a + 12.00 D. sphere was 2/60. The retina was detached below.

December 21, Shortening of Lower Half (fig. 1 *B*): The inferior rectus was resected, with excision of a piece of muscle. A 2 mm. strip of sclera was removed.

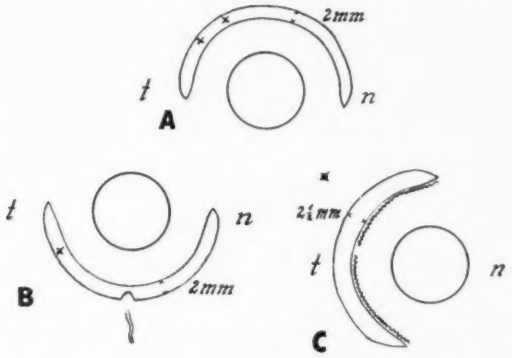

Fig. 1 (case 1).—*A*, Oct. 23, 1940; *B*, Dec. 21, 1940; *C*, Nov. 27, 1941.

One puncture of the exposed choroid provided sufficient drainage. A small piece of sclera was left because of the presence of a vortex vein.

Feb. 2, 1941: With a + 20.00 sphere vision was 6/36. There was a detachment below.

November 11: With + 20.00 D. sphere vision was 1/60. There was a detachment below.

Nov. 27, 1941, Shortening of the Outer Half (fig. 1 *C*): The excision of a strip 2.5 mm. in width was performed behind the hardly visible scar of the former shortening operations. One perforating coagulation placed temporally and above provided sufficient drainage.

December 12: Vision was 6/36 with a + 21.00 sphere.

Feb. 10, 1942: With a + 20.00 sphere vision was 6/18. The lower part of the retina was detached. The retina became entirely reattached and remained so, but the function of the lower part of the retina did not return.

Jan. 21, 1943: With a + 21.00 sphere vision was 6/24.

March 28, 1944: With a + 20.00 sphere vision was 6/18. The retina was totally attached. A third of the upper field was defective.

On last examination, on May 5, 1948, vision with a + 21.00 sphere was 6/24. The field was unchanged; the retina was attached.

The patient has been able to study and is now a teacher in a high school.

Case 2.—Michel T., aged 32, from Sofia, Bulgaria, was referred by Dr. Levieff, with typical Marfan's disease. The right eye had had a total detachment of the retina for four years, of unknown cause. Operation had been performed three times, without result. Vision was equal to perception of hand movements at 1.25 meters. Detachment appeared in the left eye in September 1941.

Examination on Oct. 9, 1941 revealed slight hydrophthalmos, iridodonesis and a shrunken lens floating in the lower half of the vitreous. A small retinal hole lay temporally and above.

Oct. 15, 1941, First Operation: Coagulations were made around the hole, without result.

November 4: The operation was repeated. The macula became attached; the retina in the temporal periphery was slightly detached.

Dec. 2, 1941: Vision with correction was 6/8.

February 1942: The retina, including the macula, was detached in the lower half; no hole was visible; vision was reduced to 6/36.

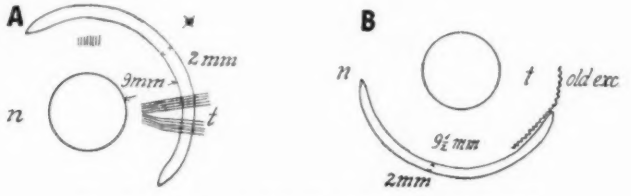

Fig. 2 (case 2).—*A*, Feb. 20, 1942; *B*, Aug. 25, 1942.

Feb. 20, 1942, First Shortening (fig. 2 *A*): A strip 2 mm. wide extending from the upper nasal to the lower temporal quadrant, was excised. The superior rectus was temporarily divided. The external rectus was tenotomized to facilitate the shortening beneath the muscle. One perforating coagulation was performed above and temporally; this had to be reopened again, as the drainage had stopped.

April 1, 1942: Vision with correction was 6/18?

Aug. 13, 1942: Vision was much poorer; with a + 12.00 sphere it was 2/36.

Aug. 25, 1942, Second Shortening (fig. 2 *B*): A strip 2.5 mm. wide was excised in the lower half. No note on the effect of the perforating coagulation was made.

Oct. 15, 1942: Vision with a + 8.00 sphere was 6/18. The retina below was slightly detached.

April 23, 1943: Vision was again reduced, being limited to counting fingers at 6 meters. The lower half of the retina, including the macula, was detached.

A careful search at this time revealed two small holes quite peripherally at the 10:30 meridian.

May 5, 1943: The holes were sealed by several coagulations.

June 29, 1943: Vision with correction was 6/12. A small area of retina was detached in the lower periphery. The field for red was contracted above; the field for movements was normal.

The patient used stenopeic spectacles until January 1947. A line of demarcation developed at the border of the remaining detachment. The patient was not cured, but he considers that his eye has healed and he lives a normal life.

CASE 3.—Ivan, A., aged 13, from Sofia, Bulgaria, who was referred by Dr. Balabanova, had been struck five years before by a piece of wood in the left eye and the eye had become blind. Three months before I saw him a similar injury occurred to the right eye.

Examination revealed total detachment, especially temporally, with flat detachment of the macula. From the disk strands extended toward the temporal portion of the retina (after hemorrhage?), where they were attached. No hole was visible.

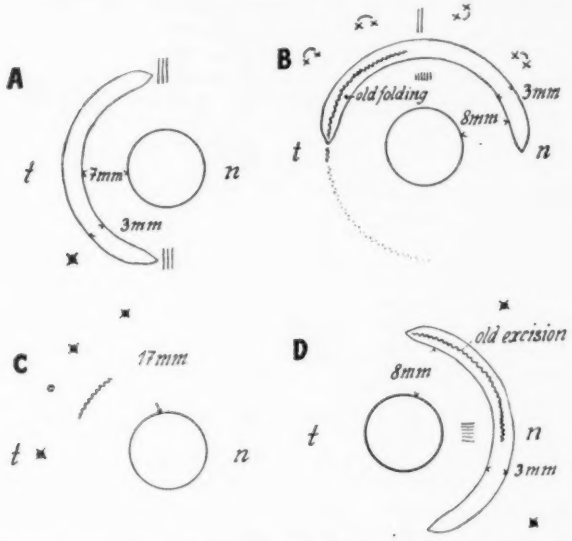

Fig. 3 (case 3).—*A*, Nov. 4, 1946; *B*, May 31, 1947; *C*, June 24, 1947; *D*, July 27, 1947.

There was a detachment of the vitreous in front of the retina at a distance which was comparable to the thickness of the lens. Vision was limited to counting fingers at 1.5 meters.

As reattachment of the retina seemed impossible on account of the strands and as no hole could be found, I had the idea of folding the sclera after thinning it and of approximating the inflamed choroid to the immobilized retina.

Nov. 4, 1946, Shortening of the Eye by Folding (fig. 3*A*): The sclera was thinned along a strip of 3 mm. This scleral membrane was then touched with 3 per cent potassium hydroxide to produce inflammatory changes in the choroid. The normal edges of the scleral wound were sutured together. One perforating coagulation was done, temporally and below.

June 16, 1946: Vision with — 8.00 sphere was 3/24. In the extreme periphery a protruding scleral fold was visible. The retina seemed to be in contact with the choroid.

May 1947: The detachment was again visible. The scleral wall had disappeared; the detachment was unchanged, and no hole was visible.

May 31, 1947, Shortening Operation (fig. 3*B*): The upper half of the eye was shortened in the usual way by excision of a strip 3 mm. wide. The scleral fold had totally disappeared; the sclera was stretched smooth, and the former thinned sclera had normal thickness. Hence, the folding operation was of no lasting effect.

June 24 (fig. 3*C*): The retina remained detached in the temporal half. To bring it into contact with the choroid, I made four trephinations in the temporal half and touched the exposed choroid with 4 per cent potassium hydroxide; then I perforated three, the fourth was bleeding and was therefore not perforated. There was no change.

June 27, Shortening (fig. 3*D*): I excised a strip 3 mm. wide in the nasal half. Two perforating coagulations were made nasally above and nasally below.

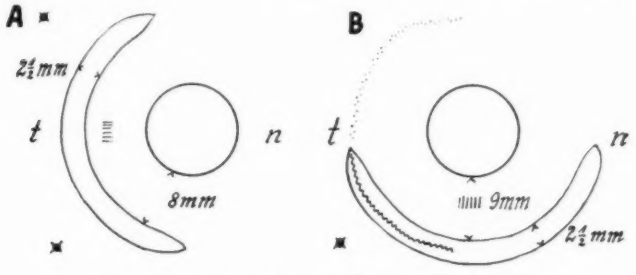

Fig. 4 (case 4).—*A*, June 4, 1944; *B*, June 14, 1944.

The retina was reattached. Vision with a — 10.00 sphere was 6/36. The field was normal at last examination, by Dr. Balabanova, in June 1948.

Case 4.—Ruth H., aged 25, became blind in her left eye as a result of uveitis in her ninth year. Iritis occurred in the right eye in 1940. The eye healed in a short time. In September 1943 there was disturbance of vision after a fall, and on October 1943 the diagnosis was detachment, with a flap hole temporally and above. Three electrocoagulations were performed.

On the first examination, May 29, 1944, a bullous detachment was found everywhere except in the area of operation, temporally and above. In this area there were old choroidal patches. The vitreous was detached half way, with a single prolongation behind the detachment line. Vision was reduced to light perception. No hole was visible.

June 5, 1944, Shortening Operation in Temporal Half (fig. 4*A*): A strip 2.5 mm. wide was excised from 6.30 to 11 o'clock, with two perforating coagulations. The first, temporally and above, did not fistulate, but the second, temporally and below, fistulated well.

June 14, 1944: The detachment became flat in the middle part. Vision with — 6.00 sphere was 2/36.

June 24, 1944, Shortening Operation (fig. 4 *B*): A strip 2.5 mm. wide comprising the lower half was excised; this included the scar of the former shortening. One perforating coagulation temporally and below fistulated well. The retinal detachment became very flat on the temporal side. Far in the periphery two single holes were discovered at 9 and 10 o'clock (Dr. Heinz).

June 22, 1944: Closure of the two holes was made with four coagulations. The retina became totally reattached.

July 26, 1944: Vision was 6/36 with a — 3.00 sphere.

Vision gradually improved. At the last examination (1947), by Dr. Marchesani (Hamburg), vision with correction was 6/18.

In this case the retinal holes were visible only after the second shortening.

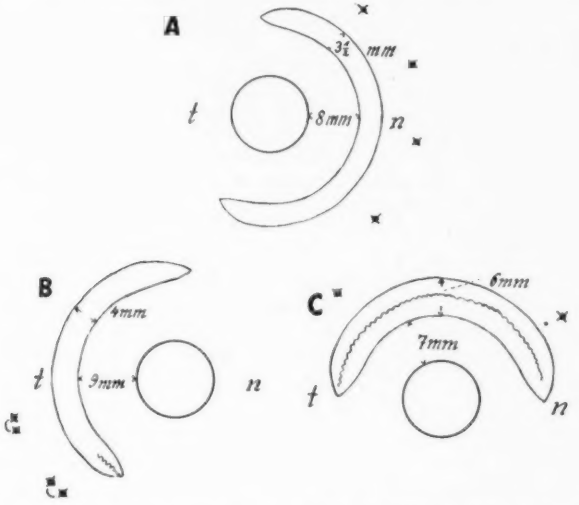

Fig. 5 (case 5).—*A*, May 4, 1946; *B*, Dec. 20, 1946; *C*, Nov. 15, 1947.

Case 5.—Agnes D., aged 24, had a retinal detachment in the left eye which had appeared one year before. There was a high myopia of — 20 D. Peripheral holes were present temporally and below. Cure was effected by one operation on Aug. 20, 1946. With a — 25.00 sphere vision was 6/60. Degenerative changes were present in the macula. Detachment for one week had been present in the right eye.

June 17, 1946: Examination revealed a nearly complete detachment. There were a large peripheral tear in the retina and a single hole temporally and below. Vision with a correction of — 15 sph. ⊃ — 2 cyl. was 3/36 —.

Two operations. on June 25 and July 23, 1946, in the neighborhood of the holes failed to affect the detachment. There was a bullous detachment; no hole was to be found.

May 5, 1946, Shortening Operation (fig. 5 *A*): A strip 3.5 mm. wide was excised from 12 to 7 o'clock. Four perforating coagulations were made posterior to the excised area. The lower half of the retina remained detached, including the macula.

Dec. 20, 1946, Shortening Operation (fig. 5 *B*): A strip 4 mm. wide was excised from 6:30 to 12 o'clock. It was difficult to apply the sutures in the area of former coagulations. The scar which resulted from the former shortening was excised. Two double pins of Safar were inserted, and good fistulation resulted.

Jan. 7, 1947: The retina was nearly attached. Vision with a — 14.00 sphere was 2/36. After a short time the detachment became more extensive.

Dec. 15, 1947, Shortening of the Upper Half (fig. 5 *C*): The old shortening scars were excised in a strip 6 mm. wide. The first perforating coagulation, temporally and above, did not fistulate. The second, nasal and above, fistulated for some time, but then the outflow stopped. The anterior chamber was punctured, and the wound reopened several times.

Jan. 16, 1948: The retina was slightly detached, nasally and down; the macula was attached. Vision with — 10.00 sphere was 6/60. The macula was degenerated.

May 13, 1948 (Last Examination): Vision with a — 10.00 sphere was 6/60. The retina showed a flat detachment below; the macula was attached. There was slight enophthalmos. The field for hand movements was nearly normal, and there is a small field for blue. If the detachment increases again and includes the macula, a fourth shortening should be performed.

COMMENT

In describing these few cases, I feel like an oculist who mentions good cases of corneal transplantation and omits those in which the operation was harmful. Therefore I shall add the results of a statistical study of two years (1944 and 1945), which will be published later in detail.

During these two years. the shortening operation has been performed on 36 eyes at this clinic. At the time of the patients' discharge from the hospital 6 eyes were cured; 10 were improved; the condition of 9 was unchanged, and that of 11 was worse. Twenty eyes have been shortened once; 12, twice, and 4, three times. On account of the war and the present political conditions, only a part of the patients could be reexamined two or three years later. Four of the 6 cured patients were reexamined and had remained cured; the others (foreigners) did not return or answer letters. But 2 other patients, not cured before, came back with reattached retinas. The majority of the patients who were not cured and whom we could reexamine had become worse. For instance, 2 patients with but one eye who left the clinic with a small area of detachment and with fairly good vision came back with a total detachment. Hence, patients not completely cured should remain under observation for years (cases 1, 2 and 5), as initial improvement may be lost. As a rule, only patients with but one eye are willing to cooperate in this way. However, sometimes they cannot continue to stay under

observation because of the expense, especially in the case of foreigners. We instruct these patients to return at once if the condition of the eye should become worse.

If the upper part of the retina remains attached, the preservation of the lower field and the prevention of complicated cataract, or of other unfavorable sequelae, would qualify even a single operation as serving its purpose. One should not forget that all these eyes were considered practically lost and would have become worse.

In several of the eyes which were cured the improvement of function was slow. As a rule, when the retina had been detached for a long time, one year is required for the final functional result.

The shortening of the globe is a difficult and a tiring operation. But the patients with but one eye whom we save from total blindness (cases 1, 2, 3 and 4) repay us for the unsuccessful operations.

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BILATERAL TOTAL OPHTHALMOPLEGIA WITH ADENOMA OF THE PITUITARY GLAND

Report of Two Cases; an Anatomic Study

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THE DIAGNOSIS of adenoma of the pituitary gland usually is made on the basis of one or more of three signs: changes in vision and visual fields, alterations in the sella turcica as demonstrated in roentgenograms and evidences of dyspituitarism. Until relatively recently cranial nerve palsies have not received the consideration they merit. During 1940 two noteworthy papers appeared, and they merit particular attention in this regard. Weinberger, Adler and Grant,[1] after reviewing 169 case records of verified adenomas of the pituitary gland, selected 14 cases which exemplified involvement of the cavernous sinus; they stated that these 14 cases by no means represented the total incidence of palsies of the cranial nerves within the cavernous sinuses in the cases they studied. Jefferson [2] described the symptomatology associated with extrasellar extensions of pituitary adenomas. A further communication containing detailed descriptions already available in these two papers would be superfluous. However, in neither of these papers or in the English literature, so far as I am aware, has there been mention of bilateral total ophthalmoplegia associated with pituitary tumor. During the past year I have observed a case of such a condition (courtesy of Dr. H. G. Johnson) and have notes on a second case which was identical as regards the ophthalmoplegia (courtesy, Dr. J. G. Arnold Jr.). A report of these cases is the primary purpose of this paper. An effort is also made to further understanding of the signs of pituitary tumor without restating what has been described authoritatively in the two papers selected for particular mention.

This paper contains (1) the findings in summary form in 50 consecutive cases of verified pituitary tumor seen in the Johns Hopkins Hospital; (2) a brief report of 2 cases of bilateral ophthalmoplegia (in this section two figures taken from Jefferson's paper [2] are included;

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital.

1. Weinberger, L. M.; Adler, F. H., and Grant, F. C.: Primary Pituitary Adenoma and the Syndrome of the Cavernous Sinus: A Clinical and Anatomic Study, Arch. Ophth. **24**:1197-1236 (Dec.) 1940.

2. Jefferson, G.: Extrasellar Extension of Pituitary Adenomas, Proc. Roy. Soc. Med. **33**:433-458, 1940.

they explain the mechanics of the sudden loss of vision which occurred in case 2); (3) a diagram which illustrates the possible routes of spread of adenoma of the pituitary gland; (4) a drawing of the cavernous sinus, and (5) comments on involvement of the fifth nerve as part of the syndrome of the cavernous sinus, as well as on loss of the corneal reflex.

FINDINGS IN FIFTY CONSECUTIVE VERIFIED CASES OF PITUITARY TUMOR

The frequency with which cranial nerve palsies and other signs occur with pituitary tumor is indicated in the following tabulation:

Types of Tumor: Adenoma, 46; carcinoma, 4	No. of Cases	Percentage
Loss of vision or changes in the visual fields	49	98
Dyspituitarism (loss of libido; amenorrhea; acromegaly)	17	34
	9	18
Diplopia, history of; absence of manifest palsy	16	32
Paralysis of ocular muscles, one or more (including 2 cases of bilateral ophthalmoplegia)	6	12
Third nerve	5	10
Fourth nerve	2	4
Fifth nerve (loss of corneal sensation)	1	2
Sixth nerve	3	6
Nystagmoid movements	2	4
Proptosis	2	4
Papilledema	4	8
Involvement of frontal lobe	2	4
Involvement of temporal lobe	1	2
Pressure on brain stem and cerebellum	1	2
Spread into sphenoid sinus and nasopharynx	1	2
Cerebrospinal rhinorrhea	1	2
First Symptoms or Signs in Series		
Loss of vision	26	52
Acromegaly	8	16
Headache	7	14
Cessation of menses; loss of libido	7	14
Diplopia	3	6
Involvement of fifth nerve	0	0

Comment.—This series is small and consequently is not statistically of value. The incidence of carcinoma of the pituitary gland is unusually high. Also, loss of vision or changes in the visual fields occurred in this series of cases oftener than in other series of verified cases. The frequency of diplopia is in accord with what has been described by Cushing [3] and the observers already mentioned. It is undoubtedly true that if careful inquiry were made in every case of pituitary tumor it would be found that in about half the cases diplopia had been present at some time.

REPORT OF TWO CASES

CASE 1.—J. A., a man aged 51, had exhibited evidences of acromegaly for twenty years. He suddenly experienced excruciating pains in the head and face and within a few hours exhibited bilateral total ophthalmoplegia. There was no demonstrable involvement of the fifth nerve; the corneal sensitivity remained

3. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

normal in both eyes. Roentgenograms revealed enlargement of the sella turcica with erosion. Visual acuity could not be tested accurately but was approximately 20/70 and 10/200 in the right and left eyes, respectively. There were incomplete bitemporal field defects. Operation was followed, after a stormy course, by complete recovery from ophthalmoplegia and return of vision to normal levels; the fields became normal.

Twenty-five years before examination at this clinic, evidence of acromegaly—enlargement of the feet, hands and head—first made its appearance. Ten years later the patient noticed gradual enlargement of the tongue. For five years he had complained of fatigability and some loss of libido. Six months before his admission there was blurring of vision of the left eye. Two weeks before admission he complained of nausea, vomiting and generalized headache. The vomiting and headaches continued for two days, during which he noted further failure of vision and inability to open his eyes. At the end of two days he was unable to open either eye.

He showed the characteristic changes of acromegaly in the face, feet and hands, and a large tongue. The skin was soft and sallow. There was normal growth of beard but no axillary and a small amount of pubic hair.

There was complete bilateral paralysis of the third, fourth and sixth nerves. The corneal reflexes were normal. The pupils were dilated and fixed to light. There was moderate pallor of the optic disks with visual acuity of 20/70 and 10/200, respectively, for the right and left eyes. There was a defect in both temporal fields. The neurologic examination was otherwise without significance.

The usual laboratory tests yielded normal results. Roentgenograms revealed typical changes of acromegaly in the hands and feet. The sella turcica was ballooned. An electroencephalogram showed no significant abnormalities.

On Oct. 1, 1948 a transfrontal operation was performed on the left side. The left optic nerve was pushed forward by a large white-yellow mass which extended between the two nerves. The capsule of the tumor was opened, and 1.6 Gm. of solid yellow tumor tissue was removed. No cysts were encountered. There was no evidence of posterior extension of the tumor, which was a chromophobic adenoma.

A good recovery was made from the operative procedure, and on the twelfth postoperative day he was given a roentgenologic treatment (234 r). A severe reaction followed during the night. Eighteen hours later he was in deep coma. The blood sugar was 18 mg. per hundred cubic centimeters. Dextrose in sodium chloride solution was administered. For four days his condition was poor. He was given a continuous infusion of dextrose solution to maintain the blood level between 50 and 70 mg. per hundred cubic centimeters. The carbon dioxide–combining power and the chlorides, calcium, phosphorus and nonprotein nitrogen of the blood remained within normal limits. On the fifth day after the reaction a regimen of desoxycorticosterone acetate (percorten®), 5 mg., and sodium chloride 8 Gm. daily was begun. Within two days he began to improve and food was taken by mouth. A glucose tolerance test three weeks after operation and a similar test two weeks later gave normal results. The basal metabolic rate six weeks after operation was —5 per cent. Approximately one month after the onset of his metabolic crisis he maintained a normal blood sugar on a normal diet.

The ophthalmoplegia commenced to disappear on the fifth postoperative day, when he was able to abduct the right eye slightly; and within a day or two the left eye could also be abducted. Reaction to light appeared in the right pupil at this time. Three weeks after operation he could elevate the right upper eyelid, and both eyes could be abducted fully. At this time the right fourth nerve

began to function and both pupils reacted to light. Two months after operation both eyes could be opened widely and both pupils responded to light, but there was still some divergence. He was discharged from the hospital on December 2, two months after operation. Four months after operation the ophthalmoplegia had disappeared completely and there was absence of diplopia. The visual fields appeared full on the confrontation test, and the visual acuity was 20/30 for each eye. Eight months after operation the visual fields were normal, and visual acuity was 20/15 and 20/20 in the right and the left eye, respectively.

Comment.—The occurrence of bilateral total ophthalmoplegia after an episode of excruciating pain in the head and face of a patient with acromegaly who has an enlarged sella turcica suggests sudden swelling of a pituitary tumor. Such swelling usually is attributable to bleeding within the adenoma. A principal point of interest in this case was the absence of demonstrable involvement of the fifth nerve and retention of normal corneal sensitivity; this observation seems of particular importance and is further commented on subsequently. Proof that the inciting development was sudden pressure is obvious because of the complete recovery of vision and visual fields and the complete disappearance of ophthalmoplegia without evidence of the "regeneration" phenomenon in either third nerve.

It is likely that before the episode which brought him for examination this patient exhibited only acromegaly as a sign of his pituitary tumor. Probably, as a result of hemorrhage, which may have been slight, there was rapid swelling of the gland with pressure on the cavernous sinuses and on the overlying optic chiasm. Operation for removal of the tumor had the same effect as the opening of a cyst which was under pressure.

CASE 2.—A white man aged 52 considered himself perfectly well until he experienced a sudden excruciating pain in the head and face. Within forty-eight hours he exhibited total ophthalmoplegia bilaterally and had lost all vision, including the ability to perceive light. There was absence of demonstrable involvement of the fifth nerve on either side. Roentgenograms of the skull showed an enlarged sella turcica with erosion of the base. An adenoma of the pituitary gland was removed surgically. The extraocular muscles rapidly developed normal power. The patient remained permanently blind.

On Dec. 7, 1948 the patient awakened with pain in both temples and about the right eye. He complained of discomfort in his chest. During the evening there was vomiting and he became restless. On the following morning, December 8, he had pronounced photophobia and vision in the right eye was blurred. There was some drooping of the right upper eyelid. He became delirious, and late in the day he stated that he was blind. He was admitted to the University Hospital on December 9.

On admission he was totally blind and was delirious. The neck was stiff, and there was total bilateral ophthalmoplegia. The temperature was 105 F. He was completely disoriented as to time and place but responded promptly to painful stimuli. There was no weakness, atrophy, tremor or muscular fibrillation. All sensations were intact, including the responses to corneal stimulation. The tendon reflexes were equal and active. The abdominal reflexes were absent.

Blood studies showed leukocytosis (white cell count 18,700). Lumbar puncture produced fluid which contained 1,017 white cells per cubic millimeter and 122 mg. of protein and 76 mg. of sugar per hundred cubic centimeters and gave a 3 plus reaction for globulin. Smears and culture of the spinal fluid revealed no pathogens; blood cultures were sterile. Subsequent studies of the spinal fluid showed a gradual approach to normal.

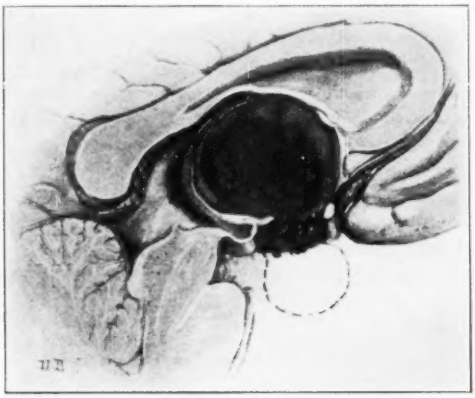

Fig. 1.—Hypothalamic extension of an adenoma, filled with blood. From Jefferson.[2]

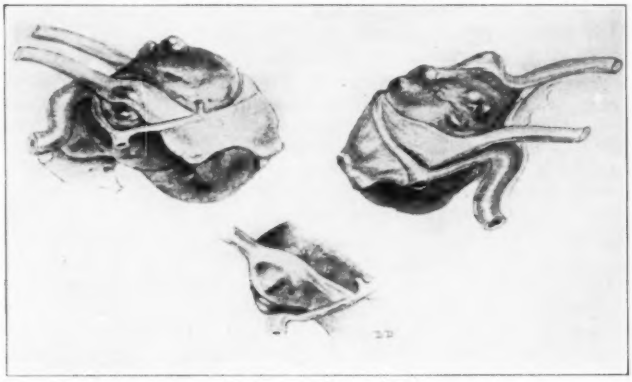

Fig. 2.—Chromophobic adenoma, with herniation of the adenoma compressing the outer fibers of the optic nerve (left eye blind). There is compression of the dorsum of the chiasma by anterior cerebral arteries. From Jefferson.[2]

Roentgenograms of the skull revealed an enlarged sella turcica, with erosion of the floor and posterior clinoid processes and sharpening of the anterior clinoid processes.

Permission for intracranial exploration was at first refused; but on December 18, at which time the ophthalmoplegia was unchanged and the patient was completely blind, a right frontal craniotomy was performed. A large adenoma of the pituitary gland was removed. Recovery from operation was uninterrupted.

On his discharge, on December 28, there had been recovery of function of the left sixth nerve and partial return of function of the right third nerve. On Feb. 15, 1949 at Dr. Arnold's office, the extraocular movements were fairly normal,

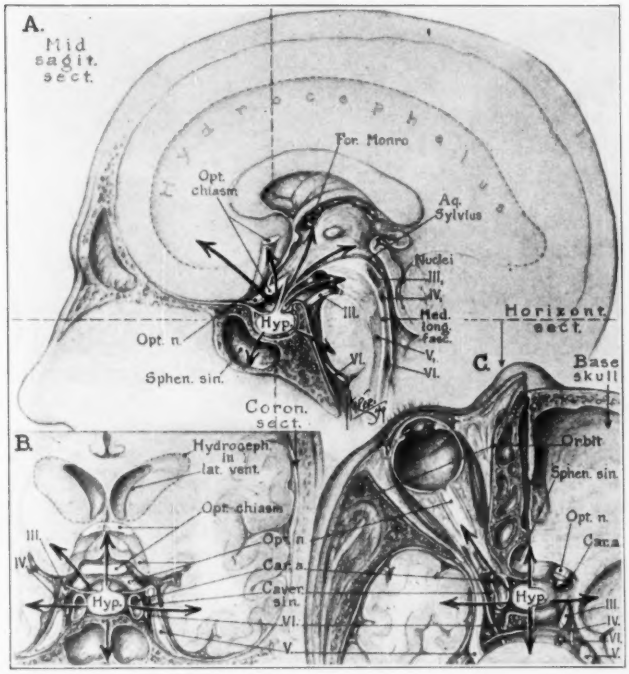

Fig. 3.—Diagram illustrating routes of extension of adenomas of the pituitary gland. Intrasellar adenomas may extend through a solid layer of bone into the sphenoid sinus (*A*). Oftener, extension is upward through the diaphragma sella, when the optic chiasm is usually affected (*A*). There may be progress forward, with involvement of the frontal lobe. The third ventricle may be filled with tumor and the foramen of Monro obstructed on one or both sides, or the aqueduct of Sylvius may be obstructed. Extension along the base may develop, as shown in *A*. Lateral spread involving the cavernous sinuses is shown in *B*. It will be noted that there is no bony wall lateral to the hypophysis (*B; A*). Obstruction to the cavernous sinuses may account for proptosis (*C*). Lateral spread accounts for involvement of the temporal lobe (*C*).

and there was movement of the pupils on attempted convergence, but the patient was quite blind.

Comment.—It is apparent that the condition in this case, except for the sudden and permanent blindness, was identical with that in case 1. Again, there was no demonstrable involvement of the fifth nerve.

The sudden loss of vision is interesting. Two figures taken from Jefferson's [2] paper explain the occurrence (figs. 1 and 2). They are included without further comment.

ROUTES OF EXTENSION OF PITUITARY ADENOMAS

Figure 3 indicates the possible extensions of pituitary adenomas. It is hoped that it may be useful in visualizing the development of signs which occasionally are associated with tumors of the pituitary gland and which cause confusion in diagnosis, namely, proptosis, hydrocephalus, ophthalmoplegia and involvements of the frontal and temporal lobes, as well as of the brain stem and cerebellum.

THE CAVERNOUS SINUS AND ITS NERVES

Figure 4 is a drawing of the cavernous sinus which has been designed to allow visualization of the arrangement of the nerves within the sinus at various levels.

RETENTION OF FUNCTION OF THE FIFTH NERVE AND THE CORNEAL REFLEX

Particular mention has been made of the absence of demonstrable involvement of the fifth nerve in the 2 cases of ophthalmoplegia associated with pituitary tumor. If pressure on the cavernous sinuses is the proper explanation of ophthalmoplegia in these cases, and it would seem to be the only reasonable explanation on the basis both of the anatomy of the parts and of the complete recovery, it is difficult to understand why the first and second division of the fifth nerve were not affected. Certainly, these sensory branches of the fifth nerve are as available for pressure as are the other (motor) nerves. With respect to this retention of function of the fifth nerve, it is obvious that the pains in the head and face are due to irritation of branches of the sensory elements of this nerve. Experimental work by Denny-Brown [4] seems to establish a factual explanation. He found that with carefully controlled cuff pressure he could abolish the function of motor nerves before that of sensory nerves. Undoubtedly, this observation applies to the nerves within the cavernous sinus; sensory nerves continue to function, since they are more resistant to pressure than motor nerves, and thus ophthalmoplegia may be complete before there is demonstrable sensory loss. The sequence of events from pressure is probably (1) paresthesias, (2) motor loss and (3) sensory loss. Thus, pressure on the cavernous sinuses

4. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, Arch. Neurol. & Psychiat. **51**:1-26 (July) 1944.

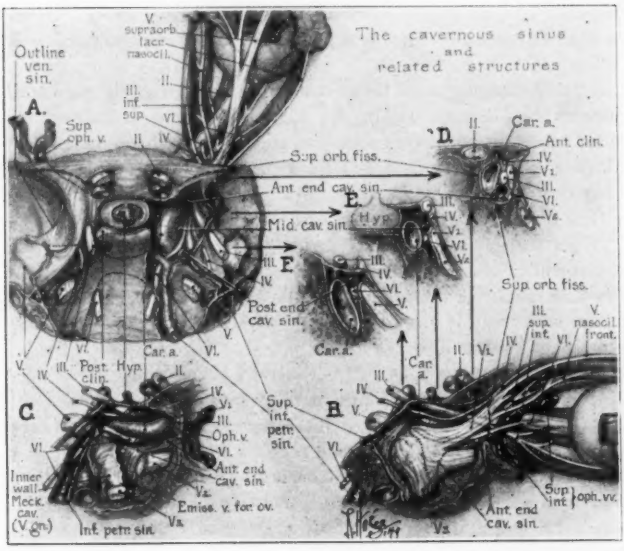

Fig. 4.—The cavernous sinus. (*A*) Top view. The dotted lines indicate the position of the sinuses. The right side is dissected. (*B*) Right lateral view. The wall of the sinus is dissected away, and the position of the nerves is shown. (*C*) Deeper dissection than that shown in *B*. The tip of the petrous bone is removed. (*D; E; F*) Vertical sections through the posterior, middle and anterior parts of the cavernous sinus, respectively.

A wide variation exists in the size and arrangement of the sinuses and the ophthalmic veins in normal persons. The superior petrosal sinus is inconstant. The intercavernous sinuses are variable in size. The transverse (basilar) sinus, which connects the inferior petrosal sinuses, is shown in *A* but is not identified in the drawing. It is always a large sinus.

Nerves in the Cavernous Sinus: The sixth nerve is shown at the base of the skull in *A*. It passes within the inferior petrosal sinus under the petrosphenoid ligament to enter the body of the sinus, where it lies lateral and inferior to the carotid artery. In *C* it can be seen that the sixth nerve enters the sinus before the third and fourth nerves. In the posterior part of the cavernous sinus only the sixth nerve and the first and second divisions of the fifth nerve are present. Farther forward in the sinus the sixth nerve becomes lateral and inferior (*E; D*). It enters the superior orbital (sphenoid) fissure inferiorly and laterally (*B; A*).

The third nerve enters the cavernous sinus at the junction of the posterior and the middle third (*F; E*). Its position anteriorly and directly lateral to the carotid artery is seen (*E; D*). It passes through the superior orbital fissure medial to and above the sixth nerve (*C; B*). This nerve divides into its superior and inferior branches within the cavernous sinus (Gifford, H., Jr.: ARCH. OPHTH. **41**:5 [Jan.] 1949); unfortunately, this is not shown in the drawing.

The fourth nerve enters the sinus just posterior to and below the entrance of the third nerve. Its course through the sinus is shown in *A*. Its position in the lateral wall of the sinus is seen in *A* and *D*. It goes through the upper part of the superior orbital fissure after passing medial to the third nerve (*B*).

The gasserian ganglion is seen to lie in Meckel's cavity (*C; B*). The sensory root and the three divisions are seen in *B*. The ophthalmic and maxillary nerves are seen to lie in the posterior part of the sinus (*B; F*). The position of the nerve in the lateral wall of the sinus is seen in *E* and *D*. The branches of the ophthalmic division are shown in *A* and *B*.

produces (1) pain in the distribution of the sensory nerves, (2) motor loss and (3) sensory loss, which in the cases here described did not develop.

If ophthalmoplegia in these cases has been properly explained as evidences of pressure within the cavernous sinus, it follows that a similar retention of sensory function and of the corneal reflex may be anticipated with anteriorly situated aneurysms and with some aneurysms within the cavernous sinus itself. The retention of the corneal reflex has been observed in many of our cases of anteriorly situated aneurysms.

When corneal anesthesia is under consideration as an evidence of involvement of the fifth nerve, it seems advisable to mention its occurrence with tumor of the cerebellopontile angle, when it is a classic sign. Corneal anesthesia is characteristically present when other evidences of involvement of the fifth nerve are not demonstrable and there is an incomplete facial nerve palsy. It is generally believed that the association of incomplete palsies of the fifth and seventh nerves accounts for the loss of the reflex, since each of these nerves forms part of the reflex arc. Thus, early loss of the corneal reflex with tumors of the angle does not contradict what has been said concerning its persistence in the cases reported in this paper.

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ACUTE TRACHOMA

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IN THOSE countries in which trachoma is epidemic and affects a high percentage of the population, infection almost always occurs in the preschool years, with an insidious onset and insignificant symptoms. Morax's early studies [1] in Egypt led him to believe that trachoma with acute symptoms was always complicated by secondary infection with one or more of the bacteria which are responsible for the acute ophthalmias, e. g., the Koch-Weeks bacillus or the gonococcus. The extraordinary prevalence and seriousness of the acute ophthalmias in Egypt have been the subject of numerous reports, and the term "ophthalmia aegyptiaca" [2] has been used to designate the acute manifestations of a conjunctivitis which is a mixture of two or of all three of the commonest infections, i. e., trachoma, gonococcic conjunctivitis and acute infectious conjunctivitis (Koch-Weeks conjunctivitis).

In those areas, however, in which trachoma is endemic only, as it is in the United States as a whole, the disease has frequently appeared to be free from secondary bacterial infection and to be acute at onset, particularly when contracted in adult life. Among the Indians of the American Southwest, on the other hand, where conditions are more like those in Egypt, the onset of the disease, which usually occurs in early childhood, seems to be almost always insidious.

The present study is an analysis of 14 cases of acute trachoma which I have observed during the course of intensive studies on the etiology and treatment of the disease in Egypt, Tunisia, Iowa, New York, Arizona, New Mexico, Florida and California.

The various criteria on which a diagnosis of trachoma may be based have been defined by many authors. In this study diagnosis depended on the gross or biomicroscopic demonstration of pannus in conjunction with at least one of the following findings: (1) follicles of the upper

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1. Morax, V.: Recherches clinique et bacteriologiques sur la conjonctivite granuleuse d'Egypte, Paris, J. Therenot, 1902.

2. Wilson, R. P.: Ophthalmia Aegyptiaca, Am. J. Ophth. **15**:397 (May) 1932.

tarsus; (2) limbal follicles or their cicatricial remains, known as Herbert's peripheral pits; (3) scarring of the upper tarsus, and (4) Halberstaedter-Prowazek inclusion bodies.

ACUTE EXACERBATIONS OF PREEXISTING CHRONIC TRACHOMA

Six cases in the series fell in this category (table 1). In 3 of them (cases 1, 2 and 5) repeated cultures revealed no evidence of secondary bacterial infection, and in 3 (cases 3, 4 and 6) there was secondary infection, with hemoglobinophilic bacteria (Koch-Weeks bacilli) in 1, with Staphylococcus aureus in another, and with Diplococcus pneu-

TABLE 1.—*Observations on 6 Patients with Chronic Trachoma with Acute Exacerbations*

Case No.	Age	Sex	Smears	Scrapings	Cultures	Preauricular Nodes	Conjunctiva	Cornea	Results of Treatment
1	55	M	Polymorphonuclear cells; no bacteria	Loaded with inclusions	Normal flora	Palpable	Papillary hypertrophy predominant	Severe epithelial keratitis	Slow improvement with copper sulfate
2	26	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Palpable	Papillary hypertrophy predominant	Severe epithelial keratitis	Rapid healing with sulfanilamide
3	10	M	Polymorphonuclear cells; pneumococci	Few inclusions	D. pneumoniae	Not palpable	Papillary hypertrophy predominant	Minimal epithelial keratitis	Healing after 30 days with sulfadiazine therapy
4	42	F	Polymorphonuclear cells; many staphylococci	Few inclusions; many cocci	Staph. aureus	Not palpable	Papillary hypertrophy predominant	Epithelial keratitis, severest below	Healing after 21 days with sulfadiazine therapy
5	22	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Not palpable	Papillary hypertrophy predominant	Severe epithelial keratitis	Rapid response to sulfadiazine therapy
6	20	M	Polymorphonuclear cells; Koch-Weeks bacilli	No inclusions seen	Hemoglobinophilic bacteria (Koch-Weeks)	Not palpable	Papillary hypertrophy predominant	Minimal epithelial keratitis	Healing after 26 days with sulfadiazine therapy

moniae in the third. The first case, observed in Iowa in 1934, was of unusual interest and may be described briefly as follows:

CASE A 1.—G. Y., a Fox Indian aged 55, had a history of trachoma of fifty years' duration. He was hospitalized with bilateral purulent conjunctivitis of extreme severity. Repeated smears showed no bacteria, and numerous cultures failed to reveal pathogenic bacteria. Epithelial scrapings, however, showed extraordinary numbers of trachoma inclusions, as many as 200 appearing in a single slide. In addition, there were masses of readily identifiable free elementary bodies, a most unusual finding in trachoma. The acute attack subsided gradually under copper sulfate therapy, leaving the previously scarred conjunctivas and corneas virtually unchanged.

This case was certainly an instance of an acute exacerbation due entirely to the virus of trachoma. In cases 2 and 5 the conditions were similar but less severe; the acute attack in each subsided rapidly on sulfonamide therapy.

Of the 3 cases in this group with secondary bacterial infection, case 6 may be considered typical.

CASE 6.—P. M., aged 26, a salesman, had acute conjunctivitis of the right eye with considerable mucopurulent exudate. There was no palpable preauricular node. In the papillary hypertrophy of the tarsal conjunctiva, which was most pronounced on the upper tarsus, buried follicles could be made out. There was a typical trachomatous pannus with scattered infiltrates and punctate epithelial lesions of the upper portion of the cornea, which were visible when stained with fluorescein. On questioning, the patient gave a history of chronic irritation of both eyes of many years' duration and stated that his mother had had irritated eyes with poor vision and ingrowing lashes.

Smears of the exudate showed polymorphonuclear leukocytes predominating, with many small, slender gram-negative rods having the morphologic appearance of the Koch-Weeks bacillus, occurring both intracellularly and free. Epithelial scrapings showed many epithelial cells with bacilli on their surfaces. No inclusion bodies were demonstrated. Cultures revealed typical hemoglobinophilic bacteria.

Oral sulfadiazine therapy was instituted, and the acute symptoms subsided rapidly. In the course of a twenty-six day period of treatment, the papillary hypertrophy disappeared; the cornea became free from subepithelial infiltrates, and the conjunctival cicatrization of stage III trachoma (MacCallan's classification [3]), previously obscured by the papillary hypertrophy, became visible. The left eye, which displayed mild stage III trachoma with pannus, healed under the sulfonamide therapy. Healing was slow, however, and there were still follicles when the sulfadiazine therapy was discontinued. These gradually absorbed over a period of weeks, until the conjunctiva had become smooth.

This case was clearly one of trachoma with acute symptoms due to secondary infection with the Koch-Weeks bacillus.

TRACHOMA OF ACUTE ONSET

Eight cases of trachoma which was acute at onset were observed in the course of this study. In 2 the disease was the result of experimental inoculations, and in 6 cases the infection occurred spontaneously. One of the 2 experimental inoculations and 1 of the 6 spontaneous infections were complicated by secondary infection with bacteria.

Experimental Inoculations (table 2).—The 2 cases in this category have already been reported.[4]

CASE 7.—The first experimental inoculation was in a young male volunteer with an incurable and eventually fatal renal disease. Epithelial scrapings from a patient with stage IIa (follicular) trachoma were brushed onto the upper and lower tarsal conjunctivas of one eye with a cotton swab. Seven days later trachoma of acute onset developed. The disease was frankly purulent. Smears showed hemoglobinophilic bacteria (Koch-Weeks bacilli), and epithelial scrapings showed typical trachoma inclusion bodies. The acute symptoms lasted about two

3. MacCallan, A. F.: Trachoma and Its Complications in Egypt, London, Cambridge University Press, 1913.

4. Thygeson, P.; Proctor, F. I., and Richards, P.: Etiologic Significance of the Elementary Body in Trachoma, Am. J. Ophth. **18**:811 (Sept.) 1935.

weeks, when typical trachoma stage IIa with early (biomicroscopic) pannus developed. This was evidently a trachoma with secondary infection from onset, and it was not possible to say whether the acute symptoms were due to the bacterial infection or to the trachoma itself.

CASE 8.—The second experimental inoculation was in a male volunteer aged 50 who had incurable carcinoma. He was similarly inoculated with a bacteria-free filtrate of pooled epithelial scrapings from patients with active trachoma. Exactly five days afterward a violently acute conjunctivitis with chemosis of the bulbar conjunctiva developed. Smears and cultures revealed no bacteria, but epithelial scrapings were loaded with inclusion bodies. The symptoms remained acute for about three weeks, when the intensity of the inflammation began gradually to subside. The first extension of limbal vessels occurred on the sixth day, and typical trachoma pannus had developed by the sixth week. The disease remained active for about a year despite intensive treatment with copper sulfate but had healed entirely at the time of the patient's death, fifteen months after inoculation. The healed conjunctiva showed extensive scarring. Secondary bacterial infection never occurred.

TABLE 2.—*Observations on Experimental Trachoma Induced in Human Volunteers*

Case No.	Age	Sex	Smears	Scrapings	Cultures	Preauricular Nodes	Conjunctiva	Cornea	Results of Treatment
7	22	M	Polymorphonuclear cells; many slender rods, like Koch-Weeks bacilli	Few inclusions Koch-Weeks bacilli	Not made	Not palpable	Papillary hypertrophy predominant	Early onset of pannus	Slow response to silver nitrate and copper sulfate therapy
8	50	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Palpable	Papillary hypertrophy predominant; chemosis of bulbar conjunctiva	Extremely severe epithelial keratitis; early onset of pannus	Slow response to copper sulfate therapy; healing in 1 yr.

Spontaneous Infections (table 3).—Of the 6 cases of spontaneous trachoma observed at onset or shortly thereafter, 3 occurred in New York, 2 in California and 1 in Arizona. Five were of white persons, and 1 was of an Apache Indian.

CASE 9.—M. G., aged 52, a New York business man, had onset of acute conjunctivitis of the right eye after a business trip west. The conjunctivitis was papillary in type and was characterized by a dense cellular infiltration of the conjunctiva, particularly intense in the conjunctiva of the upper tarsus and fornix. An intense, fluorescein-staining epithelial keratitis involved the entire surface of the cornea, but was more pronounced over the upper third. The conjunctiva of the upper limbus was edematous and infiltrated, and discharge was abundant and mucopurulent. The preauricular node was palpable but not tender. On the fourth day of the illness, minute subepithelial infiltrates were seen scattered over the upper third of the cornea but were densest close to the limbal vessels. The limbal vessels were engorged, but extension in the form of pannus was not observed until the eleventh day. The pannus developed rapidly, so that by the twentieth day examination with the slit lamp showed a typical trachomatous pannus with extension of limbal loops into the cornea around the entire circumference, but more marked above.

Cultures and smears in this case were made daily during the first weeks of the illness, but no pathogenic bacteria were found. Epithelial scrapings showed many Halberstaedter-Prowazek inclusions. These were more than twice as numerous in scrapings from the upper tarsus as they were from the lower tarsus. The exudate was always characterized by a predominance of polymorphonuclear leukocytes.

The diagnosis of trachoma in this case was based on the findings of the inclusion bodies in conjunction with corneal changes. The only disease considered in the differential diagnosis was inclusion conjunctivitis, and this could be ruled out by the presence of the keratitis and pannus.

Treatment with sulfanilamide over a period of three weeks led to healing. On examination with the slit lamp, the healed tarsal conjunctiva showed a few

TABLE 3.—*Observations on 6 Patients With Trachoma of Acute Onset*

Case No.	Age	Sex	Smears	Scrapings	Cultures	Preauricular Nodes	Conjunctiva	Cornea	Results of Treatment
9	52	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Palpable	Papillary hypertrophy predominant	Severe epithelial keratitis	Rapid response to sulfanilamide
10	38	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Palpable	Papillary hypertrophy predominant	Severe epithelial keratitis; incipient pannus	Rapid response to sulfanilamide
11	28	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Not palpable	Papillary hypertrophy predominant	Severe epithelial keratitis; incipient pannus	Rapid response to sulfanilamide
12	23	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Not palpable	Papillary hypertrophy predominant	Severe epithelial keratitis; incipient pannus	Rapid response to sulfanilamide
13	23	M	Polymorphonuclear cells; no bacteria	Many inclusions	Normal flora	Not palpable	Papillary hypertrophy predominant	Severe epithelial keratitis; incipient pannus	Rapid response to sulfanilamide
14	26	F	Polymorphonuclear cells; Koch-Weeks bacilli	Few inclusions	Hemoglobinophilic bacteria (Koch-Weeks)	Palpable	Papillary hypertrophy predominant	Mild epithelial keratitis; incipient pannus	Satisfactory response to sulfanilamide

minute scars, the cornea became free from infiltrates but the pannus vessels persisted. This case was clearly one of pure acute trachoma uncomplicated by secondary infection.

CASE 10.—G. F., aged 38, a mechanic, had bilateral conjunctivitis. The onset was acute and characterized by intense papillary hypertrophy of the conjunctiva, especially over the upper tarsus, and by mucopurulent exudation and palpable, but not tender, preauricular nodes. As in case 9, there was from onset a severe epithelial keratitis with subsequent development of subepithelial infiltrates and extension of limbal vessels. A characteristic feature of the disease was the infiltration and edema of the region of the upper limbus. This formed a sort of roll, the curve of which was easily recognizable, both grossly and with the slit lamp.

Repeated smears and cultures revealed no pathogenic bacteria, but cytoplasmic inclusions were abundant. On one slide as many as 20 per cent of the cells had

inclusions, a startling difference from the findings in any typical case of trachoma in the chronic stage.

The conjunctivitis continued in its acute phase for three weeks. Treatment with sulfanilamide was then instituted, and in three weeks the condition was healed. As the extreme papillary hypertrophy disappeared in the course of healing, follicles which had been masked by the cellular infiltration were exposed to view. After healing there was a minimal amount of conjunctival cicatrization and persistence of pannus vessels. This was evidently a case of pure trachoma of acute onset, uncomplicated by secondary infection.

Case 11.—S. F., aged 28, a salesman, had bilateral acute conjunctivitis with edema of the bulbar conjunctiva and abundant mucopurulent exudate. When seen on the third day of symptoms, the conjunctivas exhibited the heavy infiltrate and papillary hypertrophy typical of stage IIb trachoma. The preauricular nodes, unlike those in cases 9 and 10, were not palpable, but the corneas showed the same severe punctate epithelial staining. Subepithelial infiltrates were first seen on the fifth day of the illness, and extension of limbal vessels into the corneas, on the tenth day. By the eighteenth day a typical incipient pannus was demonstrable. Sulfanilamide therapy was begun on this day and was continued over a four week period. The response was rapid, and healing was obtained without difficulty.

Case 12.—A. D., aged 23, a truck driver, had onset of unilateral acute conjunctivitis. The conjunctivitis was severe, but there was no swelling of the preauricular node and the edema of the bulbar conjunctiva was limited to the region of the upper limbus. There was an unusually severe punctate epithelial keratitis with numerous subepithelial infiltrates, particularly in the pupillary area. The effect on vision was striking, the visual acuity having been reduced to 20/200 before therapy was started, on the twentieth day. Typical incipient pannus was demonstrated on the fifteenth day. A three week course of sulfadiazine led to healing and return of vision to 20/20, but nebulous scars persisted in the cornea. Smears and cultures revealed no secondary bacterial infection, but inclusion bodies were demonstrated without difficulty in epithelial scrapings until therapy was instituted. This case could be described as one of pure acute trachoma with unusual corneal manifestations.

Case 13.—D. J., aged 23, an air corps officer in active service, had onset of acute conjunctivitis of the right eye two months after returning from India. The conjunctivitis was papillary in type and displayed the thickening of the tarsal conjunctiva and the folds in the fornices which are so characteristic of viral conjunctivitis, as opposed to bacterial conjunctivitis. When the eye was first seen on the tenth day of the illness, there was already extension of limbal capillary loops into the cornea, and three days later the picture of incipient trachoma pannus was complete. No preauricular adenopathy was noted. Epithelial keratitis was severe, and subepithelial infiltrates were prominent. Sulfadiazine, begun on the twentieth day of the disease, led to rapid subsidence of the acute symptoms and to healing after a three week course. There was no evidence of secondary bacterial infection, but numerous epithelial cell inclusions were readily demonstrable. The case was clearly one of pure trachoma with acute onset.

Case 14.—F. M., aged 26, a nurse, had onset of bilateral acute conjunctivitis with slight preauricular adenopathy. There was an abundant purulent exudate, which on smear and culture revealed many Koch-Weeks bacilli. The conjunctivitis was treated daily during the first ten days with applications of silver nitrate and use of 5 per cent sulfathiazole ointment locally. When the conjunctivitis failed

to improve with this treatment, the case was restudied and evidence of an underlying trachoma deduced from the presence of typical inclusion bodies in epithelial scrapings and from corneal changes involving the region of the upper limbus. The inclusion bodies were relatively few, and the corneal changes were mild in comparison with those in the other cases in this series. Sulfadiazine therapy was instituted and improvement was noted on the third day. Healing was complete in one month. This case was evidently one of acute trachoma in which a bacterial infection contributed to the acute symptoms.

DIFFERENTIAL DIAGNOSIS OF ACUTE TRACHOMA

When the acute symptoms of acute trachoma are due to an exacerbation of previously existing trachoma, or to an acute bacterial infection engrafted on chronic trachoma, the diagnosis rests on the presence of the characteristic stigmas of trachoma, particularly cicatrization and pannus, and offers no serious difficulty. Trachoma which is acute at

Fig. 1.—Acute trachoma at onset, illustrating extreme papillary hypertrophy of the conjunctiva of the upper tarsus.

onset, on the other hand, is more difficult to diagnose and may be overlooked in this country because of its rarity.

The disease should be suspected in any case in which there are severe infiltration and papillary hypertrophy of the conjunctiva of the upper tarsus with obliteration of the conjunctival vessels and meibomian markings (fig. 1). Among the bacterial conjunctivitides, gonococcic conjunctivitis alone displays a comparably severe cellular infiltration, and in this disease the abundance of the purulent exudate is a differentiating feature. In acute trachoma the exudate is typically mucopurulent, but in the present series it was abundant only in the 2 cases complicated by infection with the Koch-Weeks bacillus (acute infectious conjunctivitis).

Differentiation from inclusion conjunctivitis appeared to offer the only serious diagnostic problem. In my experience, however, inclusion conjunctivitis, even in the acute papillary form, has not been complicated

by corneal changes, whereas in trachoma of acute onset the corneal changes have occurred simultaneously with the conjunctival changes. In this series the changes in the upper limbus, consisting in edema and infiltration of the conjunctiva at the limbus and in early extension of the limbal capillaries to form incipient trachoma pannus, were of particular diagnostic value.

Fig. 2.—Drawing of the cornea in a case of acute trachoma at onset, illustrating the punctate epithelial changes and the subepithelial infiltration so characteristic of the disease. This case was unusual with respect to the distribution of the epithelial changes, which are usually much more pronounced adjacent to the upper limbus.

Among other types of acute keratoconjunctivitis, only acute staphylococcic keratoconjunctivitis and epidemic keratoconjunctivitis would seem to need consideration in the differential diagnosis of acute trachoma. A pannus somewhat resembling trachoma pannus can sometimes develop in cases of recurrent staphylococcic infection when catarrhal infiltrates have occurred repeatedly at the upper limbus. This

is confusing, but in a staphylococcic infection there are no conjunctival scars and no inclusion bodies.

Epidemic keratoconjunctivitis would seem to be less of a problem, in view of the round corneal infiltrates which characterize it, but at least one set of investigators (Feigenbaum, Michaelson and Kornblüth [5]) have considered differentiation from this condition diagnostically important. In my experience, in only 1 case of acute trachoma was the condition clinically suggestive of epidemic keratoconjunctivitis. In this case (table 3, case 12) there were large round infiltrates in the pupillary area, but the presence of inclusion bodies and the cytologic character of the conjunctival exudate (polymorphonuclear cells predominating), as well as the rapid response of the disease to sulfonamide therapy, established the diagnosis. It is well to mention in this connection, however, that in epidemic keratoconjunctivitis with pseudomembrane formation the exudate, which is loaded characteristically with mononuclear cells, may be more polymorphonuclear than mononuclear.

In the diagnosis of questionable cases the area of the upper limbus proved to be of great interest as the site of the following lesions: (1) edema and infiltration of the limbal conjunctiva, (2) punctate fluorescein-staining epithelial lesions (fig. 2), most marked in the upper third of the cornea near the limbus; (3) subepithelial infiltrates, most prominent in proximity to the limbal vessels, and (4) extension of the limbal vessels. The region of the limbus was also one of the best sites from which to take epithelial scrapings for the demonstration of inclusion bodies.

COMPARISON OF ACUTE AND CHRONIC TRACHOMA

Acute trachoma, whether pure or with secondary infection, was characterized in this series by the extreme papillary hypertrophy of trachoma IIb (MacCallan's classification). Moreover, the acute disease apparently developed from onset as stage IIb without first passing through stage I. Follicular formation seemed to occur simultaneously, however. This was evident from the fact that cells from the germinal center of the follicles (lymphoblasts) were frequently found in scrapings from the conjunctiva of the upper tarsus, and from the fact that follicles were unmasked as the papillary hypertrophy resolved under sulfonamide therapy. In the process of healing the follicles were inevitably the last lesions to disappear, as they are in chronic trachoma.

In acute trachoma the rapidity of the response to sulfonamide therapy is striking, and in sharp contrast to the slow response of chronic follicular (stage IIa) trachoma. In chronic trachoma there is

5. Feigenbaum, A.; Michaelson, I. C., and Kornblüth, W.: Epidemic Kerato-Conjunctivitis in the Middle East, Brit. J. Ophth. **29**:391 (Aug.) 1945.

almost never any improvement in the first week; in the cases of acute trachoma in this series improvement was usually evident in three or four days and measurable at the end of the first week.

The inclusion bodies of trachoma were always numerous in the pure acute disease and were always more numerous in scrapings from the conjunctiva of the upper tarsus than in scrapings from the conjunctiva of the lower tarsus. In this respect the acute disease differed sharply from the chronic disease, in which inclusion bodies are either few or not demonstrable. For this reason, a search for inclusion bodies has limited value in cases of chronic trachoma but has very great value in cases of acute trachoma.

One of the most striking aspects of acute trachoma in this series was the rapidity with which the limbal vessels invaded the cornea. In the second experimental inoculation, vessels had penetrated the cornea by the sixth day, and at the end of six weeks extensive pannus with a pannus ulcer had developed. In chronic trachoma many months would have been required for the formation of a pannus of this extent.

The low communicability of chronic trachoma is an established fact, but if the communicability of the disease is in direct relation to the number of viral bodies demonstrable in epithelial scrapings and to the amount of mucopurulent exudate, acute trachoma should be highly communicable; and there is some epidemiologic evidence to indicate that it is.

COMMENT

The observations in this small series of cases indicate that in the United States there is a certain limited incidence of acute trachoma in which the acute symptoms are due to the trachoma virus itself. Morax's conclusion that acute symptoms in trachoma always indicated secondary bacterial infection, however applicable in Egypt, certainly does not apply in the United States as a whole. It may have a limited application in the Indian country of the Southwest, where the disease is almost always acquired in infancy and is chronic from onset. Even in the Southwest, however, I observed several instances of acute exacerbations without secondary infection in the course of a five year study of the disease among the Apache Indians at Fort Apache, Ariz.

With 1 exception, the cases in this series were of adults. From my experience, it would seem that susceptibility to the trachoma virus increases with age. This would account for the fact that trachoma contracted in infancy usually has an insidious onset and trachoma contracted in adult life an acute onset. The amount of virus in the inoculum must also be a factor. This is suggested by the observation that almost all reported experimental human inoculations of trachoma have resulted in acute infections. Of the 2 experimental inoculations

included in this series, the second, in which the inoculum was a filtrate, resulted in trachoma with an extraordinarily severe onset, the symptoms of which included chemosis of the bulbar conjunctiva.

SUMMARY AND CONCLUSIONS

Fourteen cases of trachoma with acute symptoms are reported and analyzed. In 5 of the 14 cases there was secondary bacterial infection which could have accounted for the acute symptoms, but in the remaining 9 cases the trachoma was uncomplicated. The large number of viral inclusions and the occurrence of free viral elementary bodies in the exudate in these cases suggest that the acute symptoms were due to the action of the trachoma virus itself. It is concluded that trachoma, while ordinarily a chronic disease, sometimes has an acute phase.

Pure acute trachoma in this series was characterized by extreme papillary hypertrophy of the conjunctiva, by a mucopurulent exudate with polymorphonuclear leukocytes predominating, by an abundance of cytoplasmic inclusions in epithelial scrapings and by a severe and extensive punctate epithelial keratitis.

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ENDOGENOUS INTRAOCULAR FUNGOUS INFECTION

Report of a Case

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ENDOGENOUS fungous infections of the interior of the eyes are rare. Müller (1903)[1] described metastatic nodules in the retina from miliary actinomycosis arising in the lungs. Dimmer (1914)[2] reported choroidoscleritis due to a fungus thought to be Aspergillus fumigatus. Stock (1926)[3] reported abscesses of the vitreous and retina caused apparently by identical fungi. Verhoeff (1924)[4] reported a case of uveitis caused by an actinomycete-like organism in one eye of a patient after a postoperative infection by a fungus of a similar type in the fellow eye. Verhoeff (1926)[5] also reported idiopathic retinochoroiditis caused by a similar organism occurring in a patient after a febrile illness. Churchill and Stober (1914)[6] recovered blastomycetes from the vitreous of an eye of a patient with systemic blastomycosis, but no description of the ocular lesion was given. Schwartz (1931)[7] reported hypopyon iritis in one eye caused by a blastomycete occurring in a patient with blastomycetic abscesses elsewhere in the body. Cassady (1946)[8] reported severe nodular iritis due to a blastomycete occurring in a patient with generalized blastomycosis. Archangelsky (1928)[9],

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1. Müller, L.: Ueber Veränderungen im Augenhintergrunde bei miliärer Aktinomykose, Klin. Monatsbl. f. Augenh. **41** (pt. 1): 236, 1903.

2. Dimmer, F.: Ein Fall von Schimmelpilzerkrankung des Auges, Klin. Monatsbl. f. Augenh. **51** (pt. 2): 194, 1913.

3. Stock, W.: Eine metastatische Ophthalmie durch Schimmelpilze, Klin. Monatsbl. f. Augenh. **76** (pt. 1): 49, 1926.

4. Verhoeff, F. H.: Mycosis of the Choroid Following Cataract Extraction, and Metastatic Choroiditis of the Other Eye, Producing the Clinical Picture of Sympathetic Uveitis, Arch. Ophth. **53**: 517 (Nov.) 1924.

5. Verhoeff, F. H.: A Case of Metastatic Intra-Ocular Mycosis, Arch. Ophth. **55**: 225 (May) 1926.

6. Churchill, T., and Stober, A. M.: A Case of Systemic Blastomycosis, Arch. Int. Med. **13**: 568 (April) 1914.

7. Schwartz, V. J.: Intra-Ocular Blastomycosis, Arch. Ophth. **5**: 581 (April) 1931.

8. Cassady, J .V.: Uveal Blastomycosis, Arch. Ophth. **35**: 84 (Feb.) 1946.

9. Archangelsky, W. N.: Ein Schimmelpilz unter der Netzhaut, der einen Zystizerkus simulierte, Klin. Monatsbl. f. Augenh. **81** (pt. 2): 211, 1928.

Rohner and Huber (1933)[10] and Lorenz (1933)[11] each reported a case of retinovitreous abscesses caused by an organism thought to be an aspergillus.[12] There have thus been previously reported a total of 11 cases of endogenous intraocular fungous infections, an actinomycete-like organism being causative in 3 cases, a blastomycete in 3 cases and an organism believed to be an aspergillus in 5 cases. In all but 1 case (that of Churchill and Stober) sections were examined histologically, but only in the cases of the blastomycotic infections were the lesions cultured.

The case to be reported here is also one of endogenous intraocular infection caused by an organism similar to that previously reported as an aspergillus. Like most of the other cases of aspergillar mycosis, the infection of the eye occurred in a patient who showed no evidence of fungous infection elsewhere in the body.

REPORT OF CASE[13]

History.—Z. L., a 70 year old Jewish housewife, had an uneventful medical history except for an episode several months before the ocular symptoms, when she had a cough and spat up blood-tinged sputum. The duration of this episode was only two or three days, and the incident was not considered of any importance by her physician.

The patient's ocular symptoms began with a sensation of "flies" before her left eye and, within a few hours, a sensation of a veil obscuring her vision. Whether or not the eye was red at the onset is uncertain; but when seen a few days later the eye was extremely red, and the lids of this eye were swollen. Pain was absent. There was no antecedent trauma, and, except for headaches which preceded the ocular symptoms, the patient had been in good health.

When she was seen by an ophthalmologist within two weeks after the onset, vision was nil; the conjunctiva was chemotic, and the eye was proptosed; the cornea was clear; the anterior chamber was shallow, and the ocular tension was normal. No red reflex was obtained from the fundus. The patient's temperature was not elevated, and the white blood cell count was normal. The clinical diagnosis was hemorrhage into the vitreous, but the complete loss of vision and the proptosis were unaccounted for.

The other eye was normal except for mild sclerosis of the retinal arteries.

One month after the onset severe pain developed in the eye. Examination at that time showed a steamy cornea, congested iris and extremely elevated

10. Rohner, M., and Huber, O.: Aspergillus als Ursache von Erblindung, Schweiz. med. Wchnschr. **1**: 181, 1933.

11. Lorenz, H.: Eine metastatische Ophthalmie durch Schimmelpilze, Dissertation, Munich, 1933.

12. Not included in the group is Fuchs's case of actinomycosis of the ciliary body (Ein Fall intraokulärer Aktinomykose, Arch. f. Ophth. **101**:24, 1920), since the condition is believed to have been a direct postoperative infection and, therefore, not of endogenous origin. Also not included is the report by Best (Demonstration beider durch Schimmelpilzinfektion erblindeter Augen einer Amsel, Deutsch. med. Wchnschr. **31**:1820, 1905) of an infection with A. fumigatus in the eyes of a bird because of the probable exogenous origin of the infection.

13. Dr. Frederick Salls and Dr. Benjamin Sachs furnished the clinical notes.

tension. The eye was removed. Noteworthy at the time of operation were extensive extraocular adhesions of the conjunctiva, sclera and Tenon's capsule.

The patient was last seen eight months after the enucleation. The socket appeared clean. The other eye appeared normal. The patient's general health remained good.

Pathologic Examination.—The globe was fixed in dilute solution of formaldehyde U. S. P. The globe when opened was noted to be of normal size and shape and contained a glistening white mass (presumably fat) on the episclera adjacent to the tendon of the inferior oblique muscle. When calottes were excised from

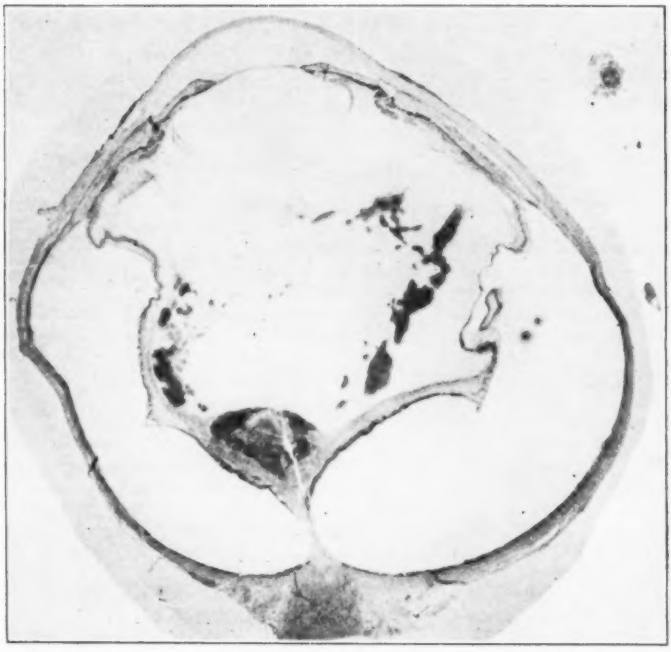

Fig. 1.—Cross section of the whole eye, showing almost complete separation of the retina with multiple abscesses on its inner surface and in the vitreous.

the upper and lower portions of the globe, the retina was seen to be partially separated and the posterior portion of the vitreous to contain a yellowish, granular material suggestive of abscess. The anterior portion of the vitreous was filled with a gelatinous material containing streaks continuous with the abscesses in the posterior part of the vitreous.

The globe was embedded in pyroxylin, and horizontal cross sections were made of the entire eye in routine fashion. Portions of the posterior half of the eye were subsequently re-embedded in paraffin. The sections were prepared variously with hematoxylin and eosin, the Gram stain, Verhoeff's modified

Gram stain, thionine, Giemsa's stain, Goodpasture's crystal violet and the Ziehl-Neelsen stain.

Histologic Examination.—The specimens consisted of cross sections of an eye showing in the gross an eosinophilic material in the aqueous, complete separation

Fig. 2.—Root of iris (× 100), showing an anterior synechia, exudate on the anterior surface of the iris and in the posterior chamber and cells (epithelioid) extending through the posterior surface of the iris.

of the retina and a multilobular basophilic material on the retina and in the vitreous (fig. 1). This material was most conspicuous in front of the disk.

The cornea was normal except for the presence of white blood cells (polymorphonuclear and round cells) and macrophages adherent to its endothelial

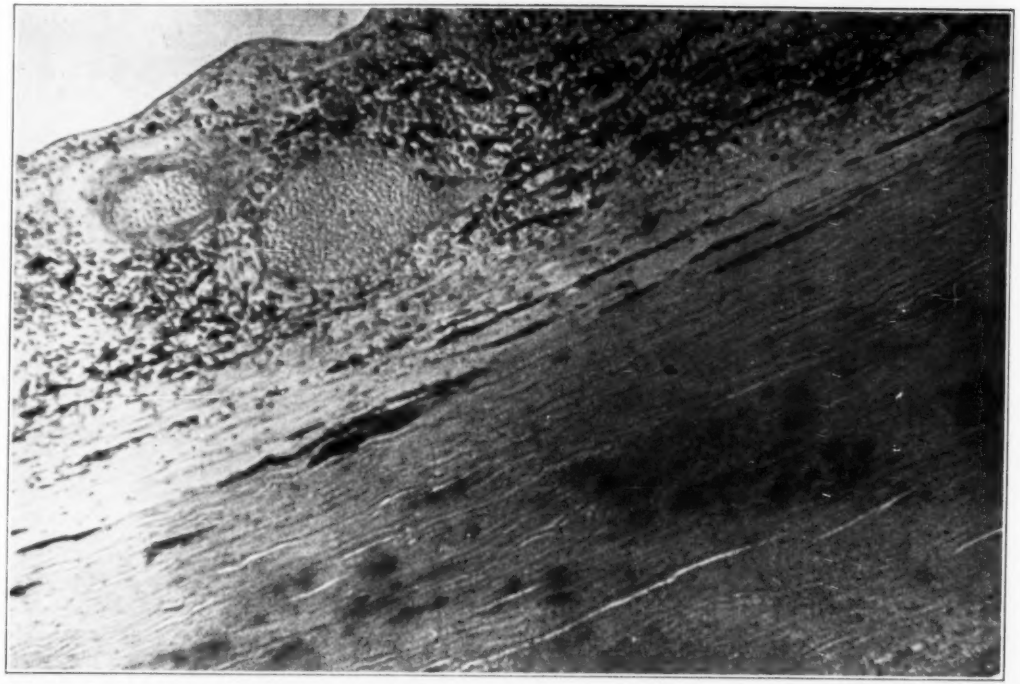

Fig. 3.—Section of choroid and sclera (× 100) in the posterior portion of the globe, showing infiltration of the choroid (chiefly by plasma cells) and calcification of the sclera.

surface. The anterior chamber was of normal depth but was filled with an eosinophilic coagulum containing fibrin and white blood cells, predominantly polymorphonuclear in type, but no giant cells. The angle of the anterior chamber was obliterated on one side by a 0.5 mm. anterior peripheral synechia and on the other side by a 1 mm. synechia; on the latter side, however, there was an open recess corresponding to the most peripheral portion of the chamber. Schlemm's canal, filled with blood, was discernible on both sides.

The iris was of approximately normal thickness but was moderately infiltrated with polymorphonuclear cells and round cells; the infiltration was considerable along the anterior surface of the iris and was especially pronounced along the posterior surface for a distance of 1 to 2 mm. from the root of the iris. Here

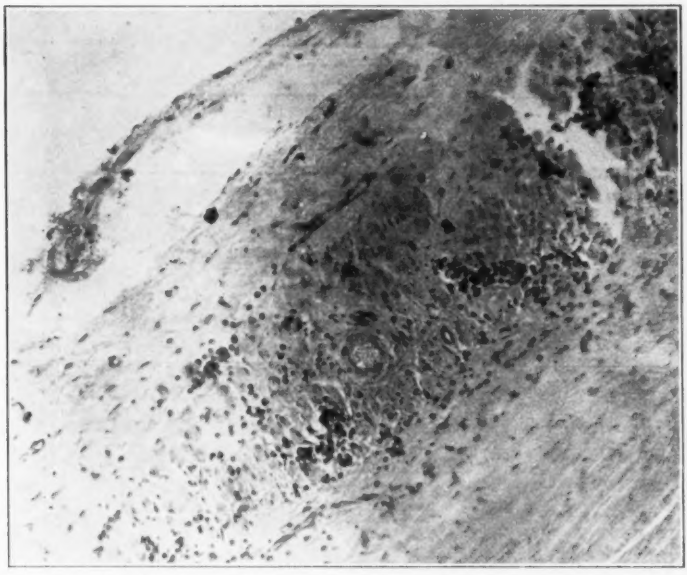

Fig. 4.—Mild infiltration of the inferior oblique muscle (by plasma cells) just behind the sclera (× 100).

the infiltrate had in some places broken through the pigment epithelium and joined with exudate in the posterior chamber (fig. 2). The infiltrate in the iris showed no predilection for the vicinity of the blood vessels. On the anterior surface of the iris on one side there was a new-formed membrane containing a blood vessel. The pupillary margin of the iris was bound to the lens by a seemingly firm posterior synechia with local disintegration of the pigment epithelium and, on one side, a backward displacement of the sphincter muscle (entropion uveae). The pupil itself was occluded by a connective tissue membrane 0.1 to 0.2 mm. thick, containing capillaries adjacent to the iris. Some sections showed the posterior part of this membrane to be undergoing a basophilic type of degeneration. The posterior chamber contained many pus cells with occasional macrophages,

fibroblasts, epithelioid cells and some fibrin. The epithelioid cells, many of which were multinucleate, were most abundant in the region of the ciliary body and gave the impression of being derived from its unpigmented epithelium; an occasional area was seen in which pyknotic nuclear material was contained within the cells of the ciliary epithelium in situ.

Fig. 5.—Dense spindle cells and a large giant cell separating the disorganized retina, in the lower part of figure, from the vitreous abscess, in the upper part of figure (× 400).

The lens was in place and showed a few morgagnian globules in its cortex but was otherwise normal.

Except for some infiltration, especially by plasma cells, some edema and hyalinization and calcification of its processes, the ciliary body was not remarkable.

Similarly, the only noteworthy changes in the choroid were edema and diffuse infiltration with plasma cells (fig. 3). Occasionally, however, the retina was fused with the choroid, and the pigment epithelium was locally destroyed. In one place an abscess from the retina had extended into the choroid, and in several

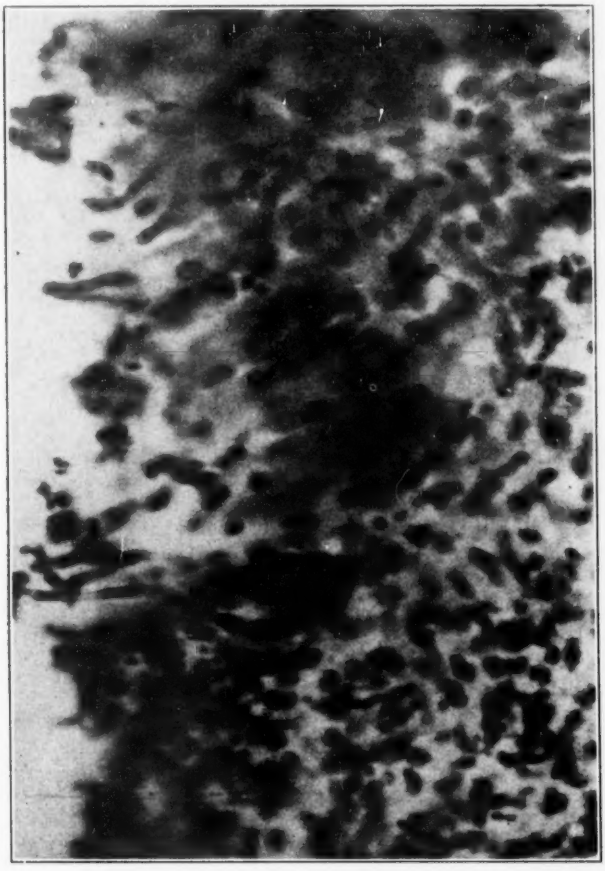

Fig. 6.—Giant cell which has been artificially separated from the abscess (left of figure), showing hyphae in the process of being phagocytosed (× 1,000).

places abscesses apparently continuous with those in the retina had lifted up the pigment epithelium.

The sclera was of normal thickness throughout, was free of infiltration but did show extensive calcification in the posterior half of the globe, especially about

the optic foramen. In the posterior portion of the eye the extraocular structures showed mild but definite infiltration with lymphocytes and plasma cells (fig. 4). This was especially evident in the portions of the oblique muscles and fat adherent to the globe. There were also some perivascular infiltration and obliterative changes in the smallest vessels.

The most significant changes were in the retina and vitreous. The retina was separated. It showed extensive edema and occasional hemorrhage, and, except for irregular persistence of the outer nuclear layer and some of the inner nuclear layer, the architecture was completely lost. The rods and cones had been com-

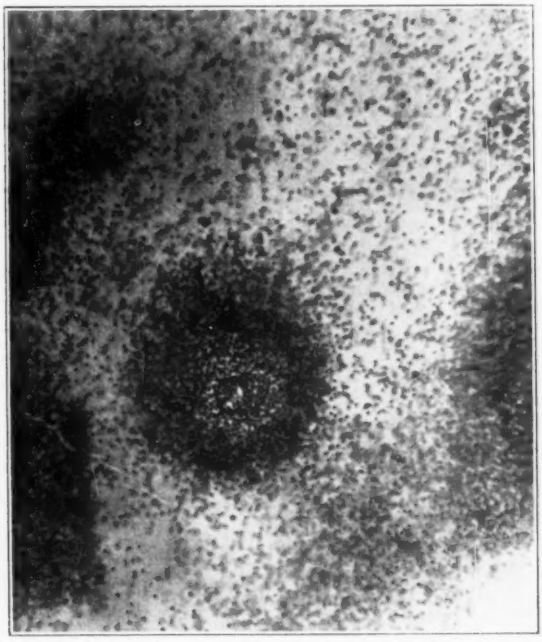

Fig. 7.—Small vitreous abscess containing a single hypha in its center (× 100).

pletely replaced by several laminas of connective tissue, to which the pigment epithelium was adherent. The innermost layer had been replaced by spindle cells, round cells (glia?) and purulent exudate. On the inner side of the retina and in the vitreous were multiple abscesses. The junction between infiltrated retina and vitreous abscess was usually abrupt, the former showing a dense membrane of spindle cells. In places these spindle cells projected into the vitreous between the abscesses, suggesting an attempt at encapsulation. Especially characteristic of the boundary between retina and abscesses was the presence of multinucleate giant cells, these cells being sometimes so numerous as to form distinct laminas (fig. 5). Some of these giant cells attained 0.1 mm. in diameter. The abscesses

tended to separate from the outer walls at the junction with the ganglion cells. Although this separation was an artefact incident to the sectioning, it was noted sufficiently often to suggest a potential line of cleavage here. It also served to

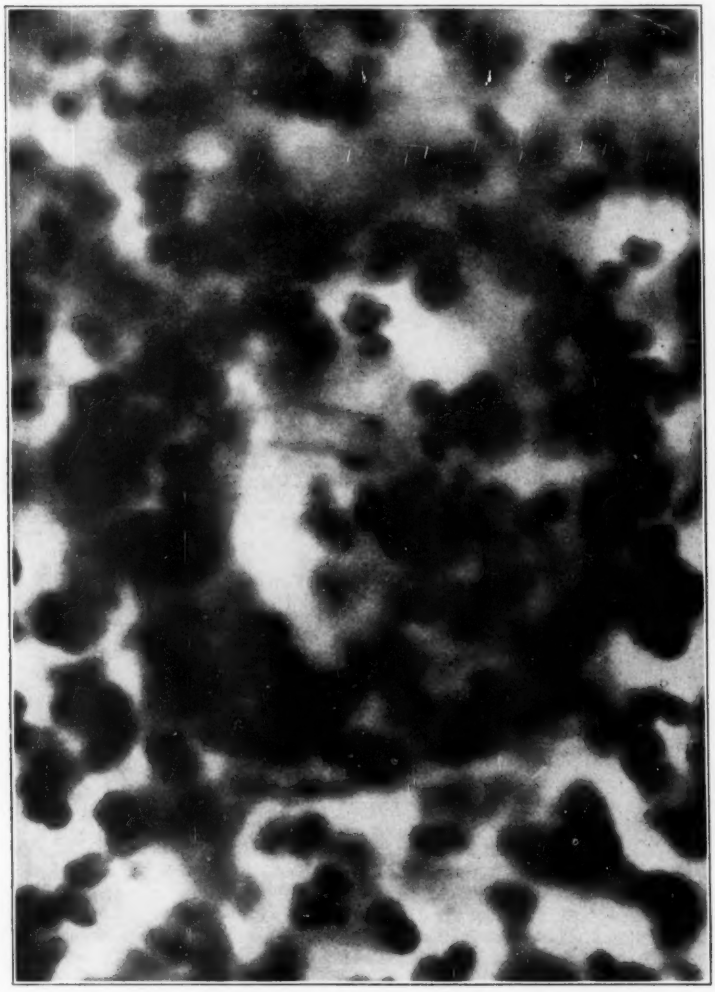

Fig. 8.—A higher magnification of the section shown in figure 7.

expose fungus particles that might otherwise have been hidden by the cellular exudate (fig. 6).

The posterior portion of the vitreous contained many small abscesses showing an occasional giant cell and many fungus organisms. The fungi tended to be centrally situated in the abscess and often surrounded a necrotic area. Frequently, a single fungus particle could be seen centrally in an abscess, surrounded by a relatively clear halo and a dark ring of cells (figs. 7 and 8). The abscesses were made up of pus cells, showing varying degrees of necrosis and occasionally

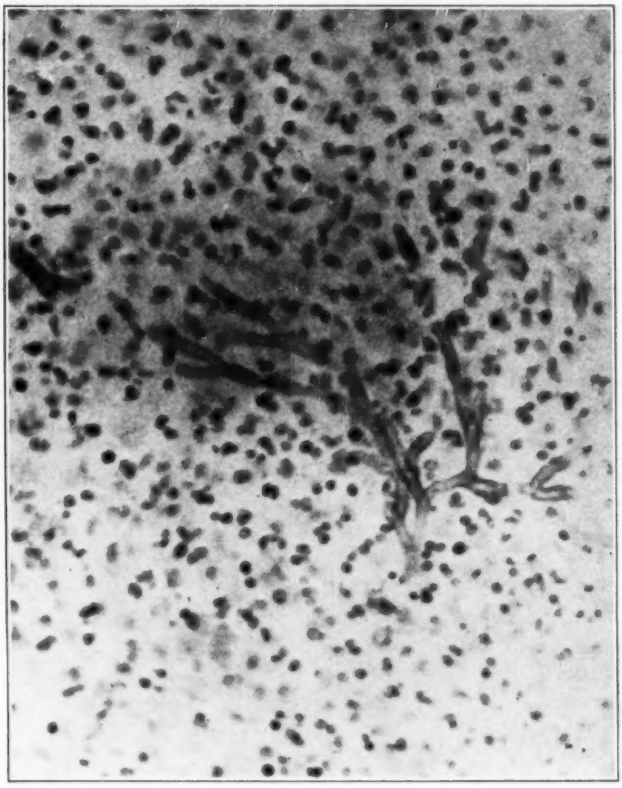

Fig. 9.—Smooth-walled fungus particles, consisting of cylindric tubes with dichotomous branches and blunt ends (× 400).

containing a giant cell. Eosinophils were rarely present. Solitary giant cells were occasionally to be seen free in the vitreous.

The fungi consisted of cylindric structures, measuring uniformly 3 microns in diameter and varying in length from 10 to 150 microns. The hyphae branched dichotomously (fig. 9). Transverse septums were rarely to be seen. The branch-

ing of the hyphae was Y shaped, and each arm of the branch had the same diameter as the stem from which it came. Usually there were not more than one or two branches for each hypha. Rarely did multiple branches come off the same place in the stem. The hyphae ended abruptly without tapering, budding or other evidence of differentiation. In the vicinity of the mycelium, and especially within its meshes, were circular, occasionally oval, bodies, measuring 3 to 4 microns in diameter and often having a thick wall (0.5 micron) and a clear, refractile center. These may have been spores but were more likely cross sections of hyphae. Both the hyphae and these circular bodies were to be seen occasionally within giant cells.

The hyphae had either cleancut walls or fuzzy, corrugated walls but tended to be uniform for any one vicinity. The former were to be found where the

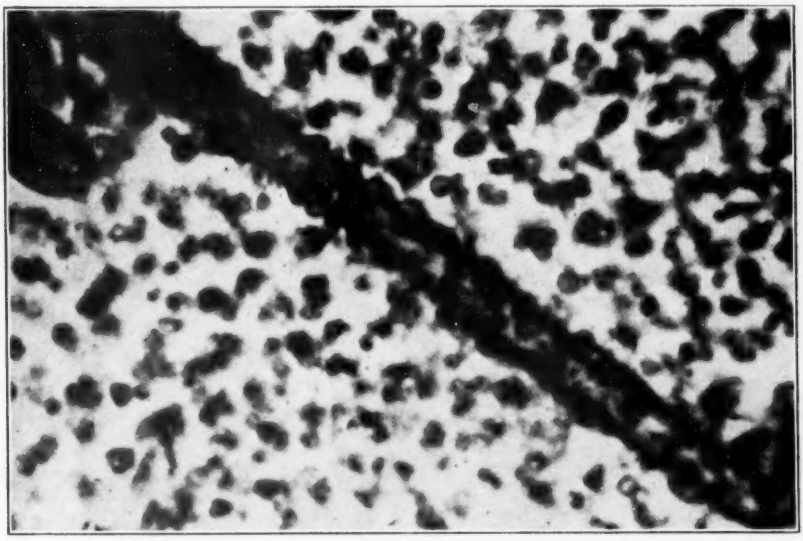

Fig. 10.—Excrescences attached to the wall of a hypha (× 1,000).

mycelium was especially abundant (rapidly growing?) and were more evident in the periphery of an abscess or in relatively cell-free areas, while the latter were to be found where the hyphae were present as short, isolated stalks (necrotic?) and were more evident in the center of an abscess.

The corrugations merit special comment. They varied from merely a pepper-like deposit on and in the vicinity of the hypha wall to gross, wartlike excrescences, obviously continuous with the wall (fig. 10). The former looked like an artefact, but the latter suggested lateral budding. This was especially true when the excrescences developed constricted necks at their point of attachment to the hypha stalk. However, these excrescences were characteristically irregular in size and shape and did not have the uniformity which one would expect if they represented true budding. They were definitely more abundant in hyphae that

were disintegrating and sometimes could be seen accompanying a fragmentation of a hypha stalk (fig. 11). With the Gram stain many such particles were to be seen in the vicinity of the fungus.

The fungus stained well with hematoxylin and could be readily seen with routine sections stained with hematoxylin and eosin or methylene blue. It was seen well also with the ordinary Gram stain, with Verhoeff's modified Gram stain and, especially, with thionine. The hyphae containing the excrescences on their walls stained much more intensely than did the cleancut hyphae. The organism stained either positively or negatively with the Gram method, depending on the intensity of the stain, but the stalk of the hypha tended to be gram-negative

Fig. 11.—Large, wartlike excrescences with apparent fragmentation of the hypha (× 1,000).

while the excrescences were gram-positive. The organism was not carbolfuchsin fast. No bacteria or other organisms were noted in any of the sections.

Especially noteworthy was the presence of yellowish brown pigment granules frequently associated with the fungous mycelium. The granules were of the same size and could not be differentiated histologically from those of the pigment epithelium. Although occasionally scattered in random fashion, the pigment granules were for the most part aggregated in spherical bodies without any capsule or other evident means of cohesion. They were to be found exclusively where the fungous mycelium was especially dense and made up of clear-walled hyphae,

as though rapidly growing. Yet the pigmented granules were most evident on the periphery, and not within the densest part of the mycelium. Especially striking was a line of mycelium and pigment granules (fig. 12), suggesting that the pigment was in fact derived from the pigment epithelium. Yet no nuclear or other cellular structure could be identified with the pigment, nor is it apparent why the mycelium should form a compact mass associated with the pigment

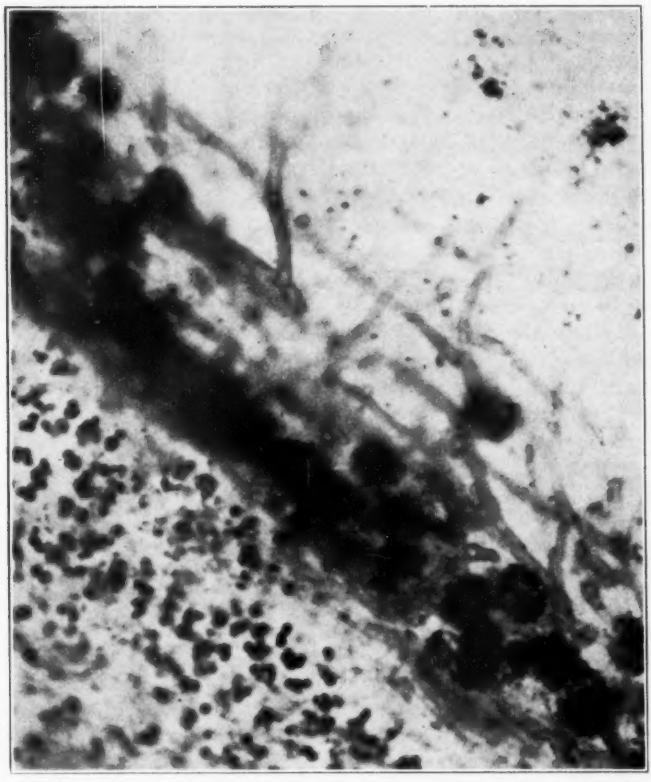

Fig. 12.—Mycelium bordering a collection of pus cells but growing freely into the vitreous and containing within its meshes spheres of pigment granules (× 1,000).

epithelium. Some fields showed the pigment granules in the periphery of the mycelium not arranged in linear fashion. These fields are what one might expect in a tissue culture and, significantly, were to be seen only in relatively cell-free areas in the vitreous.

No organisms were observed in the anterior chamber, uvea or extraocular structures, the fungi being entirely limited to the vitreous and retina.

COMMENT

To attribute the cause of the abscesses in the present case to primary fungous infection, one must exclude, first, the possiblity that the fungi occurred in the tissues as the result of postenucleation contamination and, second, the possibility that the fungi might have been secondary invaders of the eye before enucleation.

The first possibility is unquestionably disproved by the restricted localization of the fungi in the region of the abscesses and by the active phagocytosis of the fungi by giant cells. The second possibility—that the fungus was secondary to some other pyogenic excitant—cannot be disproved with certainty, but it seems most unlikely in view of (1) the nature of the granuloma, (2) the predominant orientation of the fungi within the abscesses and (3) the absence of other organisms.

Identification of the fungus must be open to question in the absence of data regarding its cultural characteristics; however, it does not appear to have been one of the common pathogenic organisms. Actinomycosis is ruled out by the absence of ray myceliums. Blastomycosis, coccidiosis and rhinosporidiosis are ruled out by the presence of a mycelium and by the absence of endospores. Histoplasmosis is ruled out by the absence of the organisms in lymph and blood vessels. The hyphae in the present case were too large to be those of Sporotrichum or Candida and too small and too regular to be those of Mucor. The remaining possibilities by exclusion are Aspergillus, which has been responsible for numerous ocular infections after perforating injuries, or some organism not ordinarily thought to be pathogenic, such as Penicillium or Hormodendron.[14]

The fungus in the present case appears to be identical with that found by Dimmer[2] in an eye with choroidoscleritis and by Stock,[3] Archangelsky,[9] Rohner and Huber[10] and Lorenz[11] in the eyes with

14. Specimens were submitted to two mycologists, and their opinions follow: Jacob Schwartz, M. D. (Harvard University) wrote: "[The specimens] show rather coarse hyphae with and without branching, both septate and nonseptate, mostly septate. There are spores, both free and attached. In one instance a broomstick-like arrangement of hyphae and spores suggests Penicillium. In several instances the arrangement of hyphae and spores suggests the genus Hormodendron. I cannot specifically identify the fungus."

Norman F. Conant, Ph.D. (Duke University): "There are indeed some branching hyphae in the abscess. It is not possible, however, to identify the fungus."

retinovitreous abscesses. All described the fungus as being approximately the same size as stated here and as having cylindric hyphae with dichotomous branching and rare, if any, septums. No definite fructification bodies were seen, and no cultures were made; but all authors stated the belief that the organism was A. fumigatus. The illustrations in their reports leave little doubt as to the morphologic identity of the fungus in these 5 cases, one with another, and with known aspergillus infections of the ocular tissues following perforating wounds [15] or experimental inoculations.[16] The unusual features of the case here reported are (1) the presence of fungus particles within giant cells, a finding not heretofore noted; (2) the presence of lateral excrescences on the walls of the hyphae, an observation noted previously once but interpreted as lateral budding, whereas the interpretation here suggested is that the excrescences are a product of disintegration of the fungus, and (3) the presence of pigment granules where the fungus is most freely growing.

These 6 cases also had clinical and pathologic features which were similar one with another and yet different from those in the other 6 cases of endogenous intraocular fungous infection, caused by an actinomycete-like organism or by blastomycetes. In only 1 of the former cases was there a systemic condition suggesting the source of the fungus, and this merely bronchitis, whereas of the 3 cases of actinomycetic infection the ocular condition followed a febrile illness in 1, was associated with frank actinomycosis of the lungs in another and followed an operation on the fellow eye in the third, and of all the cases of blastomycotic infection of the eye the condition was associated with generalized blastomycosis.

SUMMARY

Eleven cases of endogenous intraocular fungous infection have previously been reported. Of these, the causative organism was blastomycete in 3 cases, an actinomycete-like organism in 3 cases and a cylindric branching fungus thought to be A. fumigatus in 5 cases. In the present report an additional case apparently belonging to the aspergillus group is described. The onset was characterized by loss of vision, redness, chemosis and proptosis, without any evidence of systemic disease. The tension, which was low at first, became elevated, and

15. Rychener, R. O.: Intra-Ocular Mycosis, Tr. Am. Ophth. Soc. **31**:477, 1933.

16. An excellent summary of aspergillus infection of the eye may be found in Rohner and Huber.[10]

the eye was removed on account of pain. Histologically the significant feature was the presence of abscesses, with many giant cells in the vitreous and in the inner portion of the retina. In the vicinity of the abscesses, often within their centers, were the fungus particles, consisting of cylindric bodies having a dichotomous type of branching and rare septums. Excrescences on the walls of these hyphae were interpreted as manifestations of disintegration.

243 Charles Street (14).

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

National Foundation for Eye Research.—An organization known as the National Foundation for Eye Research, founded in Washington, D. C., and with offices in the Shoreham Building, proposes to raise funds for ophthalmic research. This Foundation hopes to encourage public support for medical research aimed at discovering the causes of and developing more efficacious therapies for ocular diseases leading to blindness.

The National Foundation for Eye Research will differ in its operation from many organizations designed to further medical research in that its funds will not be restricted to the study of any one disease but will be used to promote research in the whole field of ophthalmic diseases.

The activities of the Foundation will be limited entirely to supporting and establishing research centers for ophthalmology in various localities, leaving other approaches to the prevention of blindness and the rehabilitation of the blind to existing agencies.

The need for an expanded research program is apparent when one considers that there are about 260,000 blind persons in the United States, with 20,000 new cases added annually, and that the existing funds, facilities and personnel available for ophthalmic research are pitifully inadequate to study thoroughly the basic causes of the diseases which result in blindness. For instance, there is less than $400,000 spent annually in the United States on medical research primarily designed to decrease the number of blind—less than 1 per cent of that used for rehabilitation of persons who have already lost their sight. Moreover, there are only about a dozen trained, full time research men working in this field in the whole country, and few practicing ophthalmologists can devote a significant amount of time to research because of the restrictions of an active practice.

Mr. George Swartz, well known for his promotion of other medical philanthropies, has been selected as national chairman. With the assistance of a board of directors composed of prominent laymen, he will be responsible for the activities related to raising the necessary funds. The allocation of funds for research purposes will be made on the advice of a scientific advisory board, consisting of Dr. V. Everett Kinsey (chairman), Dr. Francis Heed Adler, Dr. Edwin B. Dunphy, Dr. Jonas Friedenwald, and Dr. Alan C. Woods. It is proposed to add several members to the board as the need for expansion arises.

It is hoped that ophthalmologists through their contact with the public will add their support to this group of laymen whose interest in expanding ophthalmic research has led to the formation of the National Foundation for Eye Research.

Third Annual Clinical Session of the American Medical Association.—The Third Annual Clinical Session of the American Medical Association will be held in Washington, D. C., December 6 to 9.

The Clinical Session will provide a full scale scientific program specifically designed for the general practitioner. Outstanding physicians will discuss such subjects as diabetes, pediatrics, laboratory diagnosis, physical medicine and rehabilitation, arthritis, dermatology, roentgen ray diagnosis, cancer and poliomyelitis. Coordinated with this notable scientific program will be approximately one hundred scientific exhibits which will present original work on the subjects discussed.

The newest offerings of one hundred and twenty-five manufacturing firms will comprise the Technical Exposition. Here will be found the latest developments in scientific medical research, drugs and equipment.

Televised surgical and clinical procedures, similar to those shown in color at the Annual Session of the American Medical Association in Atlantic City last June, will be presented at the Washington meeting. The demonstrations will originate in the Johns Hopkins Hospital and will be shown on screens in the Armory. The television schedule will be spread over four days.

The House of Delegates will meet at the Hotel Statler during this session. One of the first orders of business will be the annual selection of the general practitioner who has made an exceptional contribution of service to his community.

An entertainment program for attending physicians and their wives is being planned. The highlight of this program will be on Wednesday evening, December 7, when Philip Morris' "This is Your Life" will be broadcast from the Hotel Statler. The radio program will be followed by a stage show, in which outstanding stars will participate.

Blanks for hotel reservations and advance registrations may be found in *The Journal of the American Medical Association.*

Refresher Course in Ophthalmology and Otolaryngology, University of Toronto Faculty of Medicine.—The University of Toronto Faculty of Medicine offers a combined refresher course in ophthalmology and otolaryngology from Jan. 9 to Jan. 14, 1950.

The otolaryngologic subjects will be presented during the first three days of the course, and the ophthalmologic subjects, during the last three days. Lectures and surgical clinics in both fields will be given by outstanding guest speakers, as well as by members of the Faculty.

Guest Speakers are: Dr. W. J. McNally, Montreal, and Dr. Henry Orton, Newark, N. J., in otolaryngology, and Dr. P. C. Kronfeld, Chicago, and Dr. J. A. MacMillan, Montreal, in ophthalmology.

The course will be given for a minimum of 10 students and a maximum of 20 students. The fee for all or any part of the course will be $100, payable to the chief accountant, Simcoe Hall, University of Toronto.

Application should be made to the Dean of the Faculty of Medicine, not later than Nov. 30, 1949.

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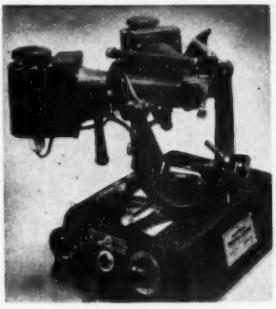

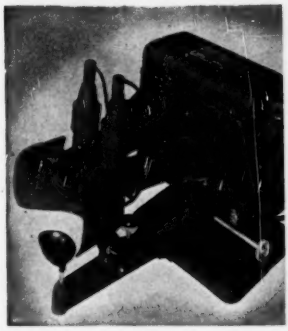

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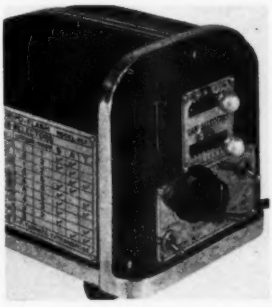

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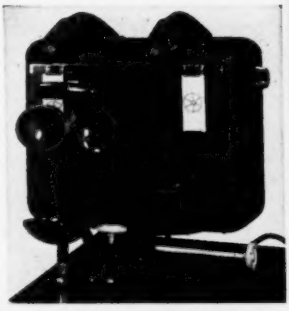

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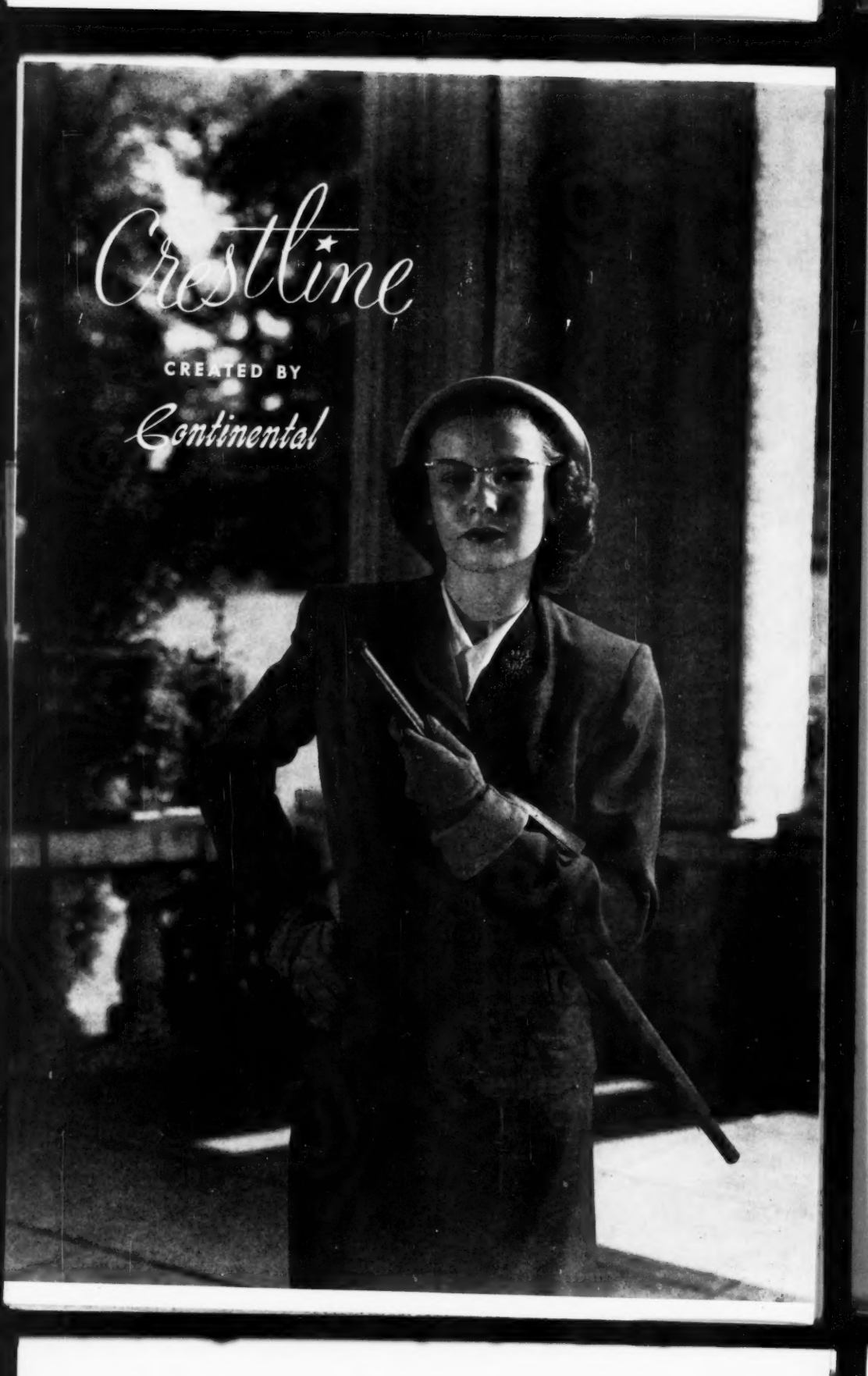
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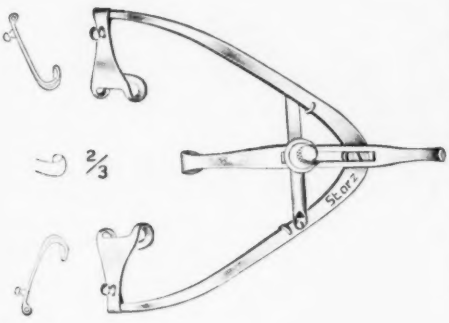

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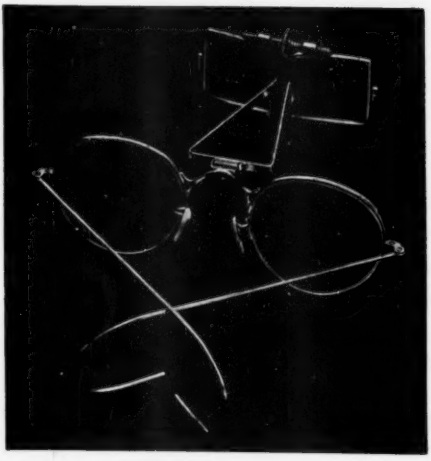

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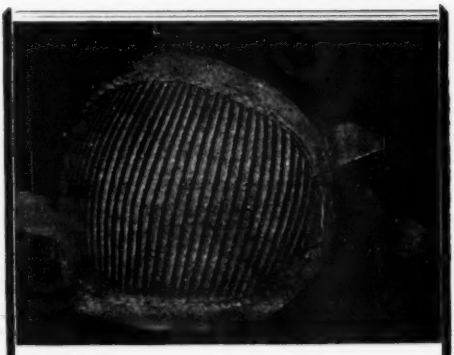

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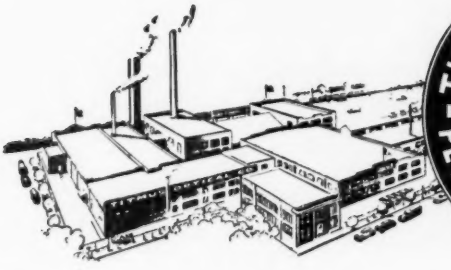

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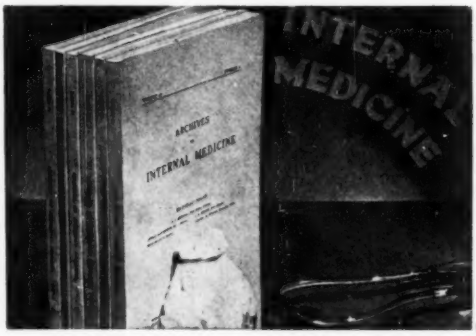

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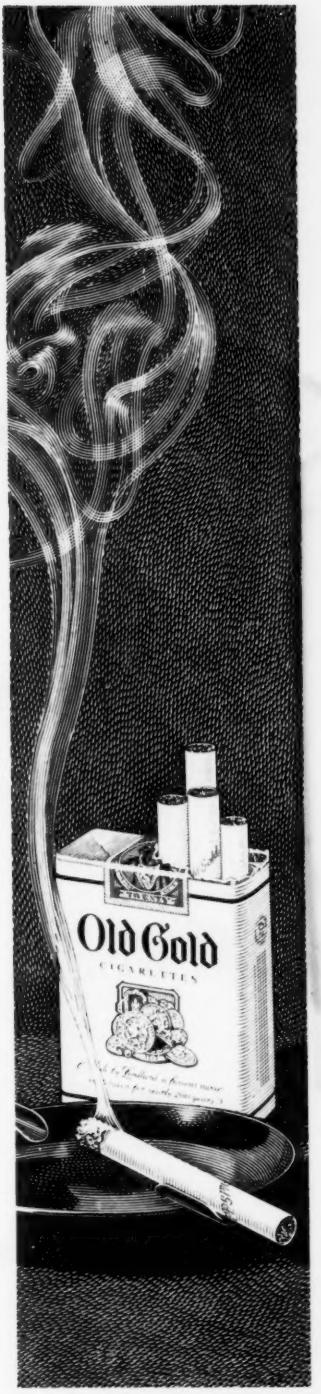

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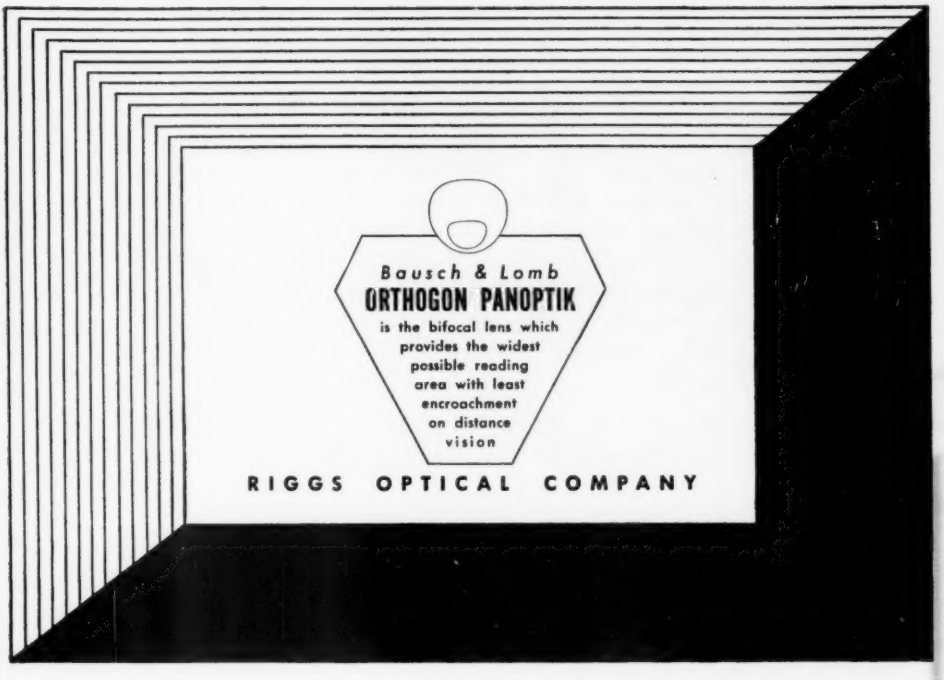
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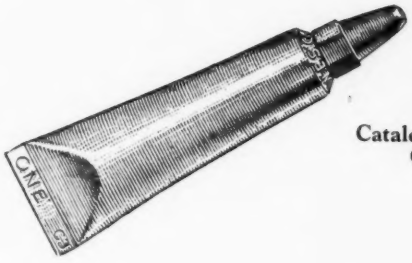

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